Title: **Pilot Study of Tissue and Hematopoietic/Mesenchymal Stem Cell Collection for Humanized Xenograft Studies in Melanoma and Squamous Head and Neck Cancer**

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BACKGROUND AND RATIONALE

Introduction

We are witnessing a fascinating era for Oncology Drug Development that is presenting us with new challenges. In one hand, there are more and more novel targeted therapies, and it is difficult to prioritize which drug is most worthy of being clinically tested. In many instances, due to the way the drug approval process is currently structured, drugs are taken to human testing with fundamental questions unanswered such as the specific target inhibited, the rational combination or the most appropriate sequencing strategy. The second major shift is the increasing demand from patients and patient advocacy groups for more personalized treatment strategies, that is, figuring out early in the drug development process what the determinants of response or clinical benefit to new (and established) drugs are. These questions are becoming more complicated as a plethora of new targets and new drugs are discovered, and it would be impossible (and also perhaps unethical) to find enough patients to answer all of these issues in a clinical setting. Currently, it takes over a decade, and over $800,000,000, to develop a drug. The basic tool for early drug development is the use of cell lines derived from tumors after hundreds of passages on artificial and simplified systems. Drugs are tested in cell lines, and then go straight to toxicology studies and human testing in phase I. There is plenty of evidence that cell lines are not predictive of what occurs is a much more complex system such as a patient. Additionally current models lack a human immune system, and the development of humanized models is an area of intense work. Unsurprisingly, nine out of ten drugs fail during this laborious, lengthy, and expensive process, and even those that pass work in only 10-20% of cancer patients and provide highly marginal clinical benefits of a few weeks/months of survival. New approaches should be explored using models that are closer to the complexities of a patient's tumor. Such a system, as described here, is considered one of the most promising of the novel approaches being explored.

The overall goal of this study is to develop a preclinical platform of melanoma and head and neck squamous cell cancer (HNSCC) that will allow us to learn more about these diseases and discover better and more individualized treatments. The principal investigator of this protocol has successfully accomplished this in other cancers (such as pancreatic, HNSCC, salivary gland and squamous skin cancer).

We implant tumors in mice because from a very small sample of tissue we can generate a much greater amount of tumor, which can be used for complex testing not possible with the small, original human sample. When they grow, the tumors will be expanded and maintained alive on mice so that we can conduct biological analyses and test anticancer drugs (some approved and in regular use, some investigational). We will learn whether there is a correlation between what happens in the patient and what happens in the patient's tumor in mice. From this we hope to learn what predicts that a patient will benefit, as we expect that some tumors will be sensitive and others resistant to each of the agents, and we will be able to identify those differential features. This will allow us to design and test individualized therapies for melanoma and HNSCC cancer in a model as close as possible to the clinical setting, thus likely preventing patients being enrolled in clinical trials with drugs that would be ultimately ineffective.

Melanoma

Melanoma causes over 8700 deaths per year in the US. Even though several small molecule targeted therapies and paradigm-changing immune modulatory agents (ipilimumab, nivolumab,

MK3475) have been developed recently (1-5), there are many unanswered questions: first, we do not understand how to individualize immune therapy for melanoma; second, we do not fully understand the molecular basis of immune response; third, we lack understanding of the interaction of immune therapies and the stroma; and finally, it is likely that there are many undiscovered immune targets.

Head and Neck Cancer

Head and neck squamous cell carcinoma (HNSCC) remains a devastating disease. The estimated combined yearly incidence in the USA is well over 50,000 new cases with over 13,000 expected deaths (6). In most instances advanced (widespread or metastatic) HNSCC or SGC is incurable, especially disfiguring and uniformly fatal. Despite a lowering tobacco consumption in recent years HNSCC incidence has not decreased and affects an increasingly younger population, due to an epidemiology shift caused by the involvement of human papilloma viruses (HPV) in their pathogenesis (7). Therefore we can only expect this disease to be a more relevant health problem in the next decades. SGC incidence remains stable.

When discovered early HNSCC has a good chance of being cured, but when it is advanced or recurs, the prognosis is very poor, being as it is a particularly disfiguring cancer. Only one agent (cetuximab) has been added to its treatment in the last 10 years (8), but the benefit is limited in intensity and in the proportion of patients that achieve it. Overall, no major advances have occurred for HNSCC patients in the last 10 years, and this is partly because there are no good preclinical models of HNSCC to study new drugs and/or new ways to deliver the right drug to the right patient. This clinical protocol is aimed at rationally generating a tool to achieve that greater goal.

Direct xenografting of patient tumors as a preclinical model for Drug Development

Freshly generated xenografted tumors have the potential to recapitulate more closely the biology of cancer than existing cell lines and are a better discriminator of the activity of anticancer drugs. The principal investigator has been involved in the generation of the largest academic mouse colony in the US, with over 200 pancreatic cancer patients consented and 80 cases successfully growing (9, 10). In addition, the PI generated a colony of 10 squamous skin cancers after implanting 15 cases of locally advanced lip, nose and face origin, highlighting the high take rate of epidermoid histologic strains (in addition to adenocarcinomas). This has allowed a variety of studies including:

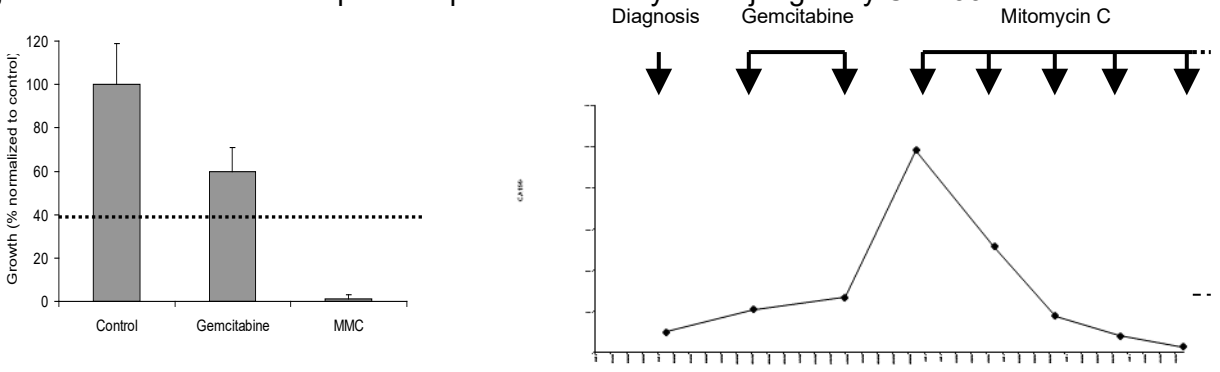
1. Development of novel diagnostic techniques: fine-needle aspiration (FNA) biopsy for drug pharmacodynamic monitoring (11) -> this is being tested in the clinic.
2. Early new drug development: testing of novel, academically-developed anticancer agents (12) -> this agent is being tested in the clinic in Phase I.
3. Complementing clinical trials: developing strategies to bridge the clinic and the laboratory (13).
4. Rational combination drug studies: testing combinations of established and investigational agents (14, 15) -> this generated two separate hypothesis that are being tested in the clinic (both at UCHSC).
5. Biomarker development: devising ways to individualize therapy by mining for biomarkers (16) -> this is being tested in the clinic in Phase II.

The common denominator of these strategies is that the laboratory findings were very rapidly translated to the clinic, so these advancements have the potential to benefit our patients sooner.

Another aspect is that the solidity of the data has allowed the generation and licensing of over 10 reports of invention and patents, highlighting the interest this strategy raises in the drug development field.

A fundamental question is whether the xenografts predict what occurs in the patient, and whether one could possibly guide patient therapy based on xenograft data. The principal investigator of this study has also been an instrumental part in the clinical trial that aimed at prospectively validating this model clinically in pancreatic cancer at Johns Hopkins (ASCO 2008, oral presentation). In that study patients were consented preoperatively and their tumors were xenografted and tested with a panel of FDA-approved agents (9). In 2 years over 200 patients were consented, and over 60 cases were successfully xenografted out of 110 implantations. This highlights the expertise, and the feasibility of this approach. In Figure 1 we can see an example (case JH033). This patient was found in the xenograft study to be resistant to gemcitabine and sensitive to mitomycin C. Unfortunately, the patient progressed prior to this data being available (with a baseline CA199 of 21,000), and received single-agent gemcitabine. He developed disease progression (with a CA199 two months later of 98,400). At that point the data became available, and the patient was treated with mitomycin C. He received 6 cycles of drug, showing clinical benefit (ECOG went from 1 to 0), a partial response radiographically, and a complete response by marker (his CA199 has dropped without a plateau to date to <40). Prior to starting MMC, the patient was declared refractory and hospice care was being discussed; on MMC he has so far been 2 years free of progression and resumed his job full-time. Though the clinical significance of this strategy remains to be proven, as more patients need to be considered, this encourages us in that these models are predictive of clinical activity of drugs, and therefore they may be more relevant for new drug development than the models currently in use.

Figure 1. Left: JH033 xenograft data, where gemcitabine shows no effect and mitomycin C shows profound antitumor efficacy. Right: Clinical course of patient JH033, where the patient progresses on gemcitabine but has a complete response to mitomycin as judged by CA-199.



PURPOSE AND OBJECTIVES

The primary objective of this study is to establish a humanized animal model. To this end, we will obtain peripheral hematopoietic/mesenchymal stem cells (HSC), blood and tumor tissue at baseline from blood and tumor samples from patients with melanoma and HNSCC who participate in the protocol at the University of Colorado Denver/University of Colorado Hospital for use in establishing tumor explants in humanized mice. Therapy results on humanized mice will be correlated with existing or newly acquired efficacy results from those same immune-based or other therapies in patients.

The secondary objective is to identify pharmacodynamic markers associated with drugs and biomarkers predictive of efficacy (or lack of thereof). To this end, and where possible, patients receiving therapy with Food and Drug Administration (FDA)-approved drugs of interest will be asked to provide sequential blood and tumor biopsies to study the molecular and immune events occurring as a result of therapy.

An exploratory objective is to assess the logistic feasibility of humanized mice to prospectively guide patient therapy decisions. To this end, the information obtained from testing the humanized mice with anti-melanoma drugs of interest may be used, at the patient's physician discretion, to guide his/her future therapy, in the context of FDA-approved indications, and/or in the context of a clinical trial, in both instances under a separate informed consent. Based on our experience, it can take between 3 and 6 months from obtaining the HSC until drug efficacy studies are complete, and therefore this warrants direct therapy guidance to be limited to an exploratory setting.

ELIGIBILITY CRITERIA

Inclusion criteria

1. Biopsy proven incurable melanoma or incurable HNSCC amenable to have biopsy and/or surgical resection of either the primary and/or locoregional metastatic site, at the University of Colorado Hospital.

2. Age ≥ 21 years old (per NCI/NIH guidelines).

3. ECOG performance status of 0, 1, or 2

4. Adequate bone marrow, hepatic and renal function:
    - Absolute neutrophil count ≥ 1,500/μL.
    - Platelets ≥ 100,000/μL.
    - Hemoglobin ≥ 9.0 g/dL.
    - Creatinine ≤ 1.5x upper limit of normal (ULN) or calculated creatinine clearance ≥ 60mL/min.
    - Total bilirubin ≤ 1.5x ULN.
    - AST/ALT ≤ 2x ULN.

5. Measurable disease according to investigator.

6. O2 saturation ≥ 93% at room air.

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

Exclusion criteria

1. Contraindication (absolute or relative) to granulocyte colony-stimulating factor (G-CSF; filgrastim) usage:
    - known hypersensitivity to E coli-derived proteins, filgrastim, or any other component of the product.
    - Sickle cell disorders.

- Clinically significant and active lung hemorrhagic or inflammatory disease, including but not limited to COPD, autoimmune disease, and alveolar hemorrhage; or hypoxemia of any etiology requiring oxygen.
- Clinically significant splenomegaly or splenic metastases; history of splenic rupture, recent splenic trauma or other clinically significant splenic disease that increases the risk of splenic rupture.

2. Clinically significant and active malignancy other than incurable melanoma or head and neck squamous cell cancer.

3. Known hepatitis B or C, or HIV.

INFORMED CONSENT

Patients with incurable melanoma or incurable HNSCC from the University of Colorado Hospital will be asked to participate in the study. Subjects will be consented by qualified study personnel, i.e., a research coordinator and/or investigator. These personnel will understand the research study and will have completed a COMIRB education course as directed by institutional requirements. The investigators, clinic nurses or research coordinator will provide the subject with information regarding the research study.

Consent will be obtained in a quiet setting prior to the initiation of any study procedures and the subject will be given ample time to consider the consent form and ask questions. Every effort will be made to ensure that the patient has an understanding of the consent formed based upon his or her verbal responses. Qualified personnel, prior to the initiation of study procedures, will obtain written consent from the eligible patient. For non-English speaking subjects, verbal translation of the consent will be provided onsite and all applicable procedures will be followed as outlined by COMIRB. The subjects will receive a signed and dated copy of the consent form.

STUDY EVENTS

Study Design

This is a study where incurable melanoma and HNSCC patients are consented to receive G-CSF in order to harvest 1) peripheral hematopoietic/mesenchymal stem cells (HSC) and blood, 2) tumor tissue, and 3) optional sequential harvests of blood and tumor samples while on anti-melanoma or anti-HNSCC therapy. The HSC will be infused into mice either freshly obtained or after stabilization in the lab to generate humanized mice. After engraftment, tumor tissue from the same patient will be implanted. Typically, it takes 4-8 weeks for HSCs to engraft and give rise to humanized mice, so there will be a lag between patient G-CSF administration/HSC collection and patient tumor biopsy implantation. These humanized mice will be studied and tested with drugs in current use for melanoma and HSNCC. Where possible, patients receiving therapy with FDA-approved drugs of interest will be asked to provide sequential blood and tumor biopsies to study the molecular and immune events occurring as a result of therapy.

This design is optimal to test the objectives of this project: The primary objective of this study is to establish humanized mice, and determine the correlation between the efficacy of immune-based and other therapy in patients and in their corresponding humanized mice. The secondary objective is to identify correlative and predictive biomarkers associated with each drug. Where possible, patients

receiving therapy with FDA-approved drugs of interest will be asked to provide sequential blood and tumor biopsies. An exploratory objective is to assess the logistic feasibility of humanized mice to prospectively guide patient therapy decisions. To this end, the information obtained from testing the humanized mice with anti-melanoma drugs of interest may be used, at the patient's physician discretion, to guide his/her future therapy, in the context of FDA-approved indications, and/or in the context of a clinical trial (in both instances under a separate consent).

Tumor, cell line generation

We will acquire normal and tumor tissue, as well as blood samples from patients. We will generate cell lines from this tissue that can include (but are not limited to):

- Cancer lines (including but not limited to cell lines and xenograft lines, if feasible).
- Blood progenitor lines (including but not limited to HSCs, PBMC, and other blood-derived progenitor lines, if feasible).
- Normal tissue lines (including but not limited to fibroblast, macrophages, if feasible)

These lines and models will be used for studies including but not limited to biology characterization, genetic characterization, and drug studies.

Study Event Summary

Events	Time point
1 - Identification and Screening	D -14 to D -1
2 - Baseline	
• Whole Blood for Genomic Testing	Prior to G-CSF Admin.
• G-CSF Administration	D1 to D4
• CBC, CMP, and AE Assessment	D6 to D7 (+/- 1 day)
• HSC Harvest	**On** D6 and **on** D7 (+/- 1 day)
• 30 Days Post-Harvest AE Assessment	D35 to 42
3 - Primary Tumor Biopsy	Before, at HSC Harvest or after
• Circ. B and T cell blood sample	At the time of biopsy
4 - Optional: Sequential Harvests for Subsequent Therapies	
• Sequential Blood Sample #1	Prior to Day 1 of New Therapy
• Sequential Tumor Biopsy #1	Prior to Day 1 of New Therapy
Note: Sequential Blood Sample #1 and Tumor Biopsy #1 are not required if no intervening therapy has occurred	
• Sequential Blood Sample #2, #3, etc.	Day 21, 42, etc. of New Therapy
• Subsequent Tumor Biopsy #2	Day 21 of New Therapy

Study Event Details

1 – Identification and Screening

Patients whom are candidates for this study will be evaluated, screened, enrolled, and followed-up at the University of Colorado Cancer Center. Informed consent will be obtained from all qualifying

patients and will be obtained by the principal investigator, a co-investigator, or a designee for this study.

Screening will consist of:
- Informed consent.
- History, physical exam, vital signs, O2 saturation, concomitant medications, and presence/grading of adverse events at baseline.
- Laboratories:
    - CBC (WBC, ANC, Hb, platelets, volume parameters, formula) and,
    - CMP (Na, Cl, K, Cr, BUN, AST/SGOT, ALT/SGPT, Alk. Phos., Protein, Albumin).

2 – <u>Baseline</u>

Whole Blood Collection for Genomic Testing

A baseline 10 mL sample of whole blood for genomic testing will be collected.

G-CSF Administration

Patients will then receive 10 µg/kg/day of filgrastim subcutaneously on a 4-day mobilization schedule. Filgrastim will be purchased at the UCH Pharmacy and provided by the study at no cost to the patient (like all other study-specific procedures). The patient will be supplied with instructions for self-administration, or administration will be arranged in clinic for them.

HSC Harvest

At the time of HSC harvest (+/- 2 days), we will draw blood for a CBC and a CMP, and conduct a follow up clinical and Adverse Event (AE) assessment with the subject.

Blood collection for HSC harvesting will occur on days 6 and 7, until a sufficient number of HSC are collected (at least 2 x 10^6), by means of a peripheral blood draw of 100 mLs of blood each day. This collection timeline will have a window of +/- 1 day. This will take place in clinic and conducted by appropriate personnel. In our experience, one draw yields 100,000 to 200,000 CD34+ HSC cells per 10 mL of peripheral blood. Thus, with a blood draw of 100 mL we expect to harvest 1 x 10^6 to 2 x 10^6 cells. We aim at obtaining at least 2 x 10^6 HSCs.

After HSC isolation, they will be infused into mice intravenously either immediately or after stabilization in the laboratory, or both. It has not been established which is the optimal method. Within this protocol we will explore various laboratory techniques to improve HSC harvest, yield, engraftment efficiency, use as allogeneic controls, and humanization to use as syngeneic hosts. We will also keep a sample from each patient cryopreserved.

Typically it takes 4-8 weeks for HSCs to engraft in mice and give rise to humanized mice, so there will be a lag between patient G-CSF administration/HSC collection and patient tumor biopsy implantation.

30 Days Post-Harvest Clinical (AE) Assessment

Approximately 30 days later (day 35 to 42) we will conduct a second clinical and AE assessment either over the phone or in person by the PI or a delegated co-investigator.

3 – Primary Tumor Biopsy

Primary Tumor Biopsy

The Primary Tumor Biopsy may occur at the time of the HSC collection, or may occur at a later time. The patient will undergo an excisional or core biopsy of the most accessible lesion in the opinion of the ENT or Cutaneous Cancer clinical providers. We will require a minimum size of 3 x 1 mm. The sample will be immediately implanted on a cohort of up to 5 mice.

Blood Collection for Circulating B and T Lymphocytes

At the time of the Primary Tumor Biopsy, a 10 mL blood sample will be drawn to determine the circulating B and T lymphocyte distribution.

The requirement of the tumor biopsy may be waived if the patient has already participated previously in a tissue banking protocol and a tumor line/xenograft is already established in the Jimeno Laboratory.

4 – Optional: Sequential Harvests for Subsequent Therapies

When the patient starts an FDA-approved anticancer treatment deemed to be of relevance by the study PI to the humanized model (including but not limited to immunotherapies, such as ipilimumab, nivolumab, and/or pembrolizumab), the patient will be asked to provide optional sequential blood samples (every 21 days after treatment initiation) and tumor samples (twice: once before new therapy and once 21 days after initiation therapy).

This sequential blood sample and tumor biopsy collection process will occur for each treatment regimen deemed to be of relevance by the study PI.

If no intervening therapy has occurred since the time of the Primary Tumor Biopsy, another baseline biopsy and blood draw will not be needed.

A separate informed consent process will occur for subsequent tumor biopsies and blood sample collections, as these procedures and assessments are part of the secondary and/or exploratory objectives of the study. Sequential biopsiable sites can include not only skin lesions, but also other sites that according to the treating physician are safely accessible (nodes, liver lesions), and that conform to the Institution's safety guidelines for sequential tumor biopsies. Thus for every therapy we will establish a (prospective or retrospective) correlation with humanized mice therapy efficacy and correlative studies.

METHODS

Generation of Tumor Explants

Aliquots from the resected tumor specimen will be implanted in nude mice using standard procedures developed by the principal investigator as detailed in the animal protocols entitled *Generation of a cancer direct xenograft colony with primary and metastatic tumors.*

Collection, Processing, and Purpose of Blood and Tissue

Note: Please use collection and processing instructions in **Appendix A**.

Whole Blood for Genomic Testing

Timepoint: Prior to G-CSF Administration
Purpose: This will be used for genomic DNA testing, and for unforeseen biomarker studies in the future. The study will analyze the different normal cells as well as their protein and genetic (including but not limited to mRNA, miRNA, methylation, DNA) profiles. This will be correlated to the same analyses in tumor cells to establish changes and correlations to help understand **cancer generation and progression**.

Whole Blood for HSC Harvesting

Timepoint: **On** D6 and **on** D7 (+/- 1 day)
Purpose: This will be used for HSC isolation, to use in humanization of mice, and for unforeseen biomarker studies in the future. The study will analyze the different normal and potentially tumor cells and cell lines as well as their protein and genetic (including but not limited to mRNA, miRNA, methylation, DNA) profiles. This will be correlated to the same analyses in normal and tumor cells to establish changes and correlations to help understand **cancer generation and progression, as well as the role of the immune system in cancer**. The cells may be propagated as isolated or after modification.

Blood Sample for Circulating B and T Cell Distribution

Timepoint: At the time of primary tumor biopsy
Purpose: This will be used to determine the circulating B and T lymphocyte distribution.

Tumor Biopsy

Timepoint: At the time of HSC Harvest or beyond
Purpose: The study will analyze the different tumor cells as well as their protein and genetic (including but not limited to mRNA, miRNA, methylation, DNA) profiles in normal and tumor tissue. The overall purpose of these studies is to determine the differences in terms of cell populations and signaling, and to **learn about the mechanisms that allow cancer cells to survive treatment**.

Optional Sequential Blood Samples

Timepoint: Prior to C1D1 of new treatment, then every 21 days thereafter (+/- 2 days)
Purpose: These samples will be used to study the molecular and immune events occurring as a result of therapy.

See Appendix A for detailed tissue and blood collection, handling, and processing instructions. Tissue samples collected will be stored frozen and in the mouse live bank indefinitely.

Optional Tissue Collection from Standard of Care Procedures

Subjects whom agree to participate in the initial part of the study will be asked to again donate tumor tissue at a later timepoint. The patient may consent to allow our team to collect additional tumor tissue if the subject is scheduled for any additional biopsies or resections as part of their regular clinical care for HNSCC or melanoma. This optional collection is outlined as an optional provision in the Main Informed Consent Form. If the patient opts to donate excess tissue from future procedures, the following samples will be collected:

Collection: Donated excess tissue from any additional scheduled biopsies or resections, as part of his/her regular clinical care for HNSCC or melanoma.

Processing: **See Appendix A.** Tissue samples collected may be implanted in mice in the Jimeno Lab following the established protocol. Tissue samples will be stored frozen and paraffin-embedded, and kept alive in the mouse live bank and as cell lines indefinitely.

Purpose: The study will analyze the different tumor cells as well as their protein and genetic profiles, and the tissue may be implanted in mice; these are identical to the testing conducted in the original sample. The overall purpose of these studies is to determine the differences in terms of cell populations and signaling, to **learn about the mechanisms that allow cancer cells to survive treatment**.

See Appendix A for tissue handling and processing instructions. Tissue samples collected will be stored frozen and in the mouse live bank indefinitely.

Optional Research Tumor Biopsy

Subjects who agree to participate in the initial part of the study will be asked to again donate tumor tissue at a later timepoint. If the subject is NOT scheduled for any additional biopsies or resections as part of their regular clinical care for HNSCC or melanoma, they will be asked to participate in a Research Tumor Biopsy. The Optional Research Tumor Biopsy will take place after a separate optional informed consent is obtained (see independent Research Biopsy Informed Consent). After optional informed consent is obtained, the following samples will be collected:

Collection: Core biopsy of tumor areas, with radiologic guidance with ultrasound if required.

Processing: **See Appendix A.** Tissue samples collected may be implanted in mice in the Jimeno Lab following the established protocol. Tissue samples will be stored frozen and

paraffin-embedded, and kept alive in the mouse live bank and as cell lines indefinitely.

Purpose: The study will analyze the different tumor cells as well as their protein and genetic profiles, and the tissue may be implanted in mice; these are identical to the testing conducted in the original sample. The overall purpose of these studies is to determine the differences in terms of cell populations and signaling, to **learn about the mechanisms that allow cancer cells to survive treatment**.

See Appendix A for tissue handling and processing instructions. Tissue samples collected will be stored frozen and in the mouse live bank indefinitely.

RECRUITMENT

Up to 40 patients locally will be recruited from the investigators' clinic at the University of Colorado Cancer Center. This figure is based on the goal to have 15 successful engrafting cases to enable meaningful biologic characterization and drug testing.

The justification for the number of successful cases required is as follows.
Since the feasibility of establishing humanized mice has not been tested prospectively, this pilot study will explore this feasibility. Since participation in this study requires patients to receive GCSFs and undergo a study-related biopsy, which are associated with more risk than minimal, we aimed at keeping enrollment in this pilot study at the minimum. If this study proves feasible, the sample size may be increased at a later time to enable full efficacy testing and patient outcomes correlations, for instance. However, at this pilot stage such studies are not feasible, and thus the sample size is largely dictated by the PI's experience with regard to the minimum sample size to determine if humanizing and conducting drug testing prospectively is a feasible strategy.

Based on the PI's experience, we do not anticipate problems of tumor availability since patients will be selected based on their willingness to undergo a biopsy and the existence of enough disease to be safely and effectively sampled. Likewise, mobilization has a greater than 95% success rate both in prior studies as well as in other settings where mobilization is standard. Therefore, we do not anticipate attrition from inability to obtain HSCs. However, **of those engrafted, 75% are a success** (defined as growth sufficient to passage further in < 6 months, and ability to be viably passaged at least three times). Thus, we will consent 20 patients per disease site (20 melanoma, 20 HNSCC) to obtain sufficient engrafted cases.

Protected health information (PHI) can be accessed by the investigators and their clinical staff or designee(s). There will be no study specific patient advertising or supplemental recruitment materials used for this study. The study will not exclude potential subjects from participation on the basis of ethnic origin or gender. Subjects recruited will include men, women and all ethnic origins, provided they meet all eligibility criteria.

DURATION OF THE STUDY

It is anticipated that this study will take up to 5 years to complete.

DISCOMFORTS AND RISKS, AND MANAGEMENT OF RISKS

The following section includes descriptions of potential risks, including risks to confidentiality.

G-CSF Administration

The risks associated with G-CSF administration in the context of mobilizing patients that are not neutropenic and are not actively receiving chemotherapy but that received filgrastim for peripheral blood progenitor cell (PBPC) collection are summarized from filgrastim's FDA label:

In clinical trials, 126 patients received filgrastim for PBPC mobilization. In this setting, filgrastim was generally well tolerated. Adverse events related to filgrastim consisted primarily of mild-to-moderate musculoskeletal symptoms, reported in 44% of patients. These symptoms were predominantly events of medullary bone pain (33%). Headache was reported related to filgrastim in 7% of patients. Transient increases in alkaline phosphatase related to filgrastim were reported in 21% of the patients who had serum chemistries measured; most were mild-to-moderate.

All patients had increases in neutrophil counts during mobilization, consistent with the biological effects of filgrastim. Two patients had a WBC count > 100,000/mm3. No sequelae were associated with any grade of leukocytosis. Sixty-five percent of patients had mild-to-moderate anemia and 97% of patients had decreases in platelet counts; five patients (out of 126) had decreased platelet counts to < 50,000/mm3. Anemia and thrombocytopenia have been reported to be related to leukapheresis; however, the possibility that filgrastim mobilization may contribute to anemia or thrombocytopenia has not been ruled out.

Other generic (not restricted to a PBPC setting) potential side effects of filgrastim include:

- Allergic Reactions. Allergic-type reactions occurring on initial or subsequent treatment have been reported in < 1 in 4000 patients treated with filgrastim. These have generally been characterized by systemic symptoms involving at least two body systems, most often skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea), and cardiovascular (hypotension, tachycardia). Some reactions occurred on initial exposure. Reactions tended to occur within the first 30 minutes after administration and appeared to occur more frequently in patients receiving filgrastim IV (which is not the route we will utilize in this protocol). Rapid resolution of symptoms occurred in most cases after administration of antihistamines, steroids, bronchodilators, and/or epinephrine. Symptoms recurred in more than half the patients who were re-challenged.
- Splenic rupture. Splenic rupture, including fatal cases, has been reported following the administration of filgrastim. Individuals receiving filgrastim who report upper left abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.
- Acute Respiratory Distress Syndrome (ARDS). Acute respiratory distress syndrome (ARDS) has been reported in patients receiving filgrastim, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Patients receiving filgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS.

Tissue Sample Collection(s)

From the perspective of the primary objective of this study that is acquiring tumor tissue there is a relatively low risk from participation in this study as the subjects as typically melanoma deposits allow

tumor acquisition with relatively low morbidity from superficial lesions. The risks associated with these procedures are infection, lack of wound healing, and local tumor spread. Tissue will only be obtained from sites that the ENT and Cutaneous Cancer Clinic physicians deem appropriate and feasible.

There is a risk that the tissue will be used up in the research activities and for some unforeseen medical reason would be needed in the future, although the biopsy is not done for diagnostic purposes since a diagnosis is already established.

Blood Sample Collection(s)

The risks of a blood sample are minimal and include pain, bleeding, bruising, infection, and skin irritation (from cleaning agents used to sterilize the skin, or bandages).

Transmissible Disease

A potential risk to clinical and laboratory study personnel is to be accidentally infected with a transmissible disease while manipulating tissue from the patient (initially, or in the laboratory studies).

Specific Anti-melanoma or Anti-HNSCC Therapies

The risks derived from receiving therapy for advanced melanoma or HNSCC are not discussed herein, since this is not a therapeutic trial, and the correlation of efficacy between the animal model and the clinic does not require prospective therapy (it could theoretically be established fully based on past therapeutic effect in the patient). Thus, any prospective therapy decision will be made by the primary physician who will contextualize the humanized mice efficacy profile, and will be made either in the setting of a FDA-approved administration as standard of care (SOC; associated with a regular SOC consent process), or under the aegis of a clinical trial (where a specific consenting will be required).

Risk Avoidance and Management

The following section includes description of procedures for protecting or minimizing potential risks including risks to confidentiality.

Patients will be carefully screened to ensure meeting all eligibility criteria. The screening criteria and study processes have been carefully designed to identify and avoid the known potential adverse events resulting from filgrastim in the PBPC setting, and also include other more generic contraindications to ensure subject safety. Patients that are not stable clinically, whose organ function is not appropriate, or who have prior conditions that put them at risk from filgrastim complications (such as lung inflammatory disease, sickle cell disease, splenomegaly or splenic abnormalities) will be excluded. After enrolment, patients will be carefully followed by clinical and study personnel to ensure that no complications arise from G-CSF administration, tumor biopsy, or blood draws. We will conduct laboratory (CBC, CMP) and clinical and AE assessment approximately one week after filgrastim administration, and then clinical assessment approximately 30 days after filgrastim administration.

From the perspective of the primary objective of this study that is acquiring tumor tissue there is a relatively low risk from participation in this study for the subjects as melanoma deposits typically

allow tumor acquisition with relatively low morbidity from superficial lesions, and HNSCC also spreads superficially to easily biopsiable node sites. Tissue will only be obtained from sites that the ENT and/or Cutaneous Cancer Clinic physicians deem appropriate and feasible. Standard of care post biopsy procedures will be followed to that effect, and there is sufficient clinical personnel and sufficient effort allocated from them to achieve this careful surveillance.

Regarding the risk that the tissue will be used up in the research activities, this risk is minimized since no usage is made of existing specimens used for clinical diagnosis, and because a trail of cryopreserved and paraffin fixed materials are generated.

Regarding the risk of transmissible disease in clinical or laboratory study personnel, risk is minimized since patients with known hepatitis B or C, or HIV are excluded from the study.

Clinical Information on study subjects will be entered in a password-protected clinical trial management system, which is a remote, firewalled system used for clinical trials at the University of Colorado. Clinical Research Assistants (CRA) are given access to specific protocol data only after special training, and each CRA has a specific login and password. Clinical data on study subjects will be maintained on this system.

All data and study records including hard copies and computer files will be considered confidential and disclosure to third parties other than those listed on the HIPAA Authorization form is prohibited. Subjects will be assigned a tissue collection number (specimen number). The utmost precautions will be taken to ensure that PHI is not compromised. Files on the computer are password protected and security is maintained by firewalls. Files containing patient data will be stored in a locked office.

Discussion of why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and in relation to the importance of the knowledge that may reasonably be expected to result.

The only anticipated benefits for the subjects for participating in this study is to learn about the susceptibility of their tumor to one or more available therapies for melanoma and HNSCC, which while it may or may not correlate with the clinical susceptibility, may inform the patient's physician about the therapy's potential efficacy. However, as the risks are moderate (bone discomfort from filgrastim administration, local pain from the biopsies, bruising from the optional blood sample among the major risks involved) we feel this is balanced.

WITHDRAWAL

Participation in this study is voluntary. At any time, the patient may withdraw participation. They must contact the principal investigator in writing. The patient's options would then be to destroy all identifying links between the patient and their tissue, and/or have their clinical tissue sent back to the original institution if any remains.

BENEFITS

There is no direct benefit to subjects for their participation in this study. However, therapeutic testing in humanized mice may identify a therapy for which the patient may be a candidate in the future (either as SOC if FDA-approved or in a clinical trial) that either works or does not work, and the patient's oncologist may help inform future treatment based on this information.

DATA ANALYSIS

The following is a non-exhaustive list including information that will be gathered at the time of study initiation:

1. Demographic information including:
    - Name
    - Medical record
    - Social Security Number
    - Telephone Number
    - Address
    - Date of birth
    - Date of diagnosis
    - Race/ethnicity
    - Gender
2. Pathologic diagnosis and specimen number
3. Prior cancer history, prior therapy, duration of therapy and best response to therapy
4. Comorbidities
5. Prior Cancer
6. Stage of Cancer
7. Metastatic sites
8. Site where specimen obtained and designation whether primary or metastatic site

The following is a non-exhaustive list including information that will be collected prospectively:

1. Outcome information such as:
    - Adjuvant therapy and dates
    - Relapse and dates
    - Therapy in the salvage setting, dates and response
    - Therapy in the advanced setting, dates and response
    - Exitus and dates
2. Long-term events and toxicities

STATISTICAL PLAN

For reporting purposes, the results will be summarized using standard descriptive statistics. Patient baseline and outcome data (in patients consenting specifically for this) will be analyzed as follows: Overall survival and progression free survival will be estimated using the Kaplan-Meier method and will be displayed graphically. Median overall survival and confidence limits will be determined. Kaplan-Meier estimates of survival at 6 and 12 months and their standard errors will be calculated. The response rate (if the patient receives therapy in the advanced setting, and disease is amenable to being evaluated) will be determined using the RECIST criteria. Comparisons between categorical groups will be conducted using the appropriate parametric or non-parametric statistical test (Chi-square, T-Student, etc.).

In order to establish the correlation between disease characteristics, engraftment success, and association with outcome measures (both in the patient and in the xenograft) a multivariate Cox model will be constructed.

The correlation between the efficacy of treatments in the xenografts and in patients (if that data exists) will be examined both as 1) a "population"-based using Spearman's and/or Pearson's tests, and 2) as a paired analysis between the efficacy in the patient and in his/her xenograft. For the correlation analyses, both the continuous response data (as % following RECIST) and the categorical response data (as YES/NO) will be analyzed and included in the multivariate model.

The animal protocol entitled ***Generation of a cancer direct xenograft colony with primary and metastatic tumors*** has an appropriate and independent statistical plan in order to rationally plan the number of animals required.

All statistical analyses will be conducted using an adequately licensed commercial statistical package.

DATABASE

A database will be developed to link pertinent information obtained from the health record of the subject, the tissue and blood specimen. HIPPA compliant data security and patient confidentiality will be achieved through use of job-specific user name/password protection (see below). Patient health data will be gathered at the time the subject's tissue is collected. Patients will be asked to consent separately (by means of an optional initialing box) to be contacted and/or for his/her clinical record to be accessed by study personnel to collect prospective data related to his primary disease (that would typically include outcome measures [recurrence, response to therapy]) in order to establish the correlation with the laboratory efficacy data. The reason prospective data is needed is two-fold:

1. We do not know whether engraftment success will be related to tumor features known at baseline (such as site of origin, histology characteristics) or whether they would relate to longitudinal features, such as local aggressiveness, metastasis frequency and location, etc. If the latter would be the case and we had the information to establish the correlation, we would likely gain a relevant insight in the mechanics of xenograft models and the biology of xenografts.
2. A secondary/exploratory objective is whether these humanized xenografts are predictive of patient response to drugs. If the latter would be the case and we had the information to establish the correlation, we would likely gain a relevant insight in the applicability of xenograft models and their potential role in individualizing therapy.

Records for this study will be maintained in password-protected computers and in locked cabinets in the Cancer Clinical Trials Office (CCTO) of the Anschutz Cancer Center or Dr. Antonio Jimeno's research laboratory. Electronic data will be kept in the standard CCTO shared drive and will be backed up with the frequency dictated by CCTO procedures. Each specimen will be given a study generated specimen number.

USE AND PROTECTION OF HEALTH INFORMATION

This project will require the use of protected health information for research purposes. A HIPPA authorization form will be provided to the subject at the time of consent. This authorization will designate the specific health information that will be required to be released.

As this project requires the use of protected health information for research purposes, a signed and dated authorization will be collected by the qualified study staff at the time the subject is consented. The protected health information that will be collected and with whom it will be shared is detailed in the Authorization to Release Medical Information form.

Clinical information regarding study subjects will not be stored within the laboratory. Rather, the password-protected clinical trial management system will be used for storage of clinical information (see below). Samples located in the lab will be labeled with HM indicating humanized mice, the tissue type and number only (e.g., the first HNSCC patient is “HM-HNSCC-001”).

CONFIDENTIALITY

All data and study records including hard copies and computer files will be considered confidential and disclosure to third parties other than those listed on the HIPAA Authorization form is prohibited. Subjects will be assigned a tissue collection number (specimen number). The utmost precautions will be taken to ensure that PHI is not compromised. Files on the computer are password protected and security is maintained by firewalls. Files containing patient data will be stored in a locked office.

DATA SAFETY AND MONITORING

The protocol will be approved and reviewed by the Cancer Center scientific review committee (PRMS).

The Principal Investigator will be responsible for monitoring the safety and efficacy of the trial, executing the DSM plan, and complying with all reporting requirements to local and federal authorities. This will be accomplished under the oversight of the Data & Safety Monitoring Committee (DSMC) of the University of Colorado Cancer Center (UCCC). The DSMC is responsible for monitoring data quality and patient safety for all clinical studies at UCCC. A summary of the DSMC activities follows:

- Conduct of internal audits
- Ongoing review of all reportable adverse events and all serious/unanticipated adverse events
- Supervises internal DSM boards and/or performs as an internal DSMB
- Has the authority to close and/or suspend trials for safety or trial conduct issues and may submit recommendations for corrective actions to the Associate Directors Executive Committee
- Performs routine internal monitoring of both investigator-initiated and cooperative group clinical trials

The PI will provide a DSM report to the UCCC DSMC on a six month basis. DSM reports will contain data from all participating sites. The DSM report will include summaries of minutes taken at monthly meetings, the participants’ demographic characteristics, expected versus actual recruitment rates,

treatment retention rates, any quality assurance or regulatory issues (including a summary of any protocol deviations), summary of AEs and SAEs, summary of dose modifications, and any actions or changes with respect to the protocol. The DSM report to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results from these reviews will be provided to all participating investigators to submit to their IRBs at the time of continuing review.

ADVERSE EVENT REPORTING

This study is an interventional, but not therapeutic, study. Due to the use of filgrastim, we will conduct clinical assessments on subjects two times following the administration of filgrastim. The PI will follow the procedures above for reporting AEs and SAEs,if any.

Definitions of Adverse Event (AE)

According to the International Conference on Harmonisation (ICH) guidelines (Federal Register. 1997;62(90):25691-25709) and 21 CFR 312.32, IND Safety Reports, and ICH E2A, Definitions and Standards for Expedited Reporting, an adverse event is defined as follows:

An adverse event is any untoward medical occurrence in a patient or clinical investigational subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Definitions of a Serious Adverse Event (SAE)

An adverse event should be classified as a serious adverse event if it meets one of the following criteria:

Fatal:	*Adverse event resulted in death*
Life threatening:	*The adverse events placed the patient at immediate risk of death. This classification did not apply to an adverse event that hypothetically might cause death if it were more severe.*
Hospitalization:	*The AE required or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not serious adverse events by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.*
Disabling/ incapacitating:	*Resulted in a substantial and permanent disruption of the patient's ability to carry out activities of daily living.*

Congenital anomaly or birth defect:	*An adverse outcome in a child or fetus of a patient exposed to the molecule or study treatment regimen before conception or during pregnancy.*
Medically significant:	*The adverse event did not meet any of the above criteria, but could have jeopardized the patient and might have required medical or surgical intervention to prevent one of the outcomes listed above.*

All AEs and SAEs, if any, will be reported to the COMIRB at the University of Colorado Anschutz Medical Campus according to institutional guidelines, and to the UCCC DSMC as stated above.

DATA PROTECTION/FIREWALLS

Clinical Information on study subjects will be entered in a clinical trial management system which is a remote, firewalled system used for clinical trials at the University of Colorado. CRA's are given access to specific protocol data only after special training, and each CRA has a specific login and password. Clinical data on study subjects will be maintained on this system.

FUNDING AND INTELLECTUAL PROPERTY

The University of Colorado School of Medicine is sponsoring this tissue collection and lab work via divisional and grant funds. The funding supports patient expenses (G-CSF, labs, exams), the blood and tissue collection, and all preclinical lab work. We anticipate that preliminary data generated from this project will lead to multiple other grant opportunities. It is possible future funding for the conduction of experiments and tests will involve collaborations with other academic medical centers, universities, or pharmaceutical/laboratory companies. We anticipate such collaborations will occur when the University of Colorado does not have the necessary expertise for specific assays, when large numbers of xenografts are needed (and therefore pooled from multiple institutions), or when costs would be prohibitive.

The Cancer Center Clinical Trials Core Grant will also be sponsoring part of this protocol. This grant will be paying for part of regulatory and coordination of this protocol.

There are no anticipated costs to the patient for participation in this research. Patients will not be paid for their participation in this study.

Intellectual property issues will be managed according to the University of Colorado Denver policies as implemented by the Technology Transfer office.

SPECIAL POPULATIONS

No special populations are targeted for accrual to this study.

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Appendix A

Blood/Tissue Collection, Handling, and Processing Instructions

Tumor samples will be obtained from consenting patients at the University of Colorado Hospital in accordance with protocols approved by the Colorado Multiple Institutional Review Board (COMIRB).

Whole Blood for Genomic Testing

Collection: 10 mL of blood in one (1) 10mL sodium heparin **green-top tube**.
Handling: Deliver samples to Jimeno Lab immediately after collection.
Processing: Put at 4C. Invert and mix. Aliquot as is in 3 cryovials.

Whole Blood for SC Harvesting

Collection: 50 mL of blood will be collected in ten (10) 10mL sodium heparin **green-top tubes**.
Handling: Deliver samples to Jimeno Lab immediately after collection.
Processing: Put at 4C. Invert and mix. Blood samples will be processed by the Jimeno lab following the established protocol.

Blood Sample for Circulating B and T Cell Distribution

Collection: 10 mL of blood in one **(1) 10mL sodium heparin green-top tube**.
Handling: Deliver samples to Jimeno Lab immediately after collection.
Processing: Put at 4C. Invert and mix. Blood samples will be processed by the Jimeno lab following the established protocol.

Optional Sequential Blood Samples

Collection: 10 mL of blood in one **(1) 10 mL sodium heparin green-top tube**.
Handling: Deliver samples to Jimeno Lab immediately after collection.
Processing: Put at 4C. Invert and mix. Blood samples will be processed by the Jimeno lab following the established protocol.

Blood for CBC and CMP

Per clinical laboratory standards.

Tumor and normal tissue from biopsy or surgical resection specimens

Collection: Excisional or core biopsy of the most accessible lesion in the opinion of the ENT or Cutaneous Cancer clinical providers. The minimum size required is 3 x 1 mm.
Processing:

- Tissue samples collected will be implanted in mice in the Jimeno Lab following the established protocol. Tissue samples will be stored frozen and paraffin-embedded, and kept alive in the mouse live bank and as cell lines indefinitely.

- For research-specific samples, after the tumor is resected samples will be taken for immediate processing, and the specimen will be delivered from the clinical or surgical suite to the study team.
- For samples taken as part of standard of care surgical or biopsy management the Pathology House Staff responsible for the specimen will guide and instruct the trial personnel in the dissection to the specimen, such that the tissue collection process in no way compromises pathologic diagnostic practice.
- The trial technical personnel will be paged ahead of time, and will be present in the clinic or grossing area.
- Fragments of tumor tissue and grossly normal tissue will be collected, each not smaller than 0.2 cm in the smallest dimension.
    - Tumor tissue. As much excess tumor tissue as possible will be collected, in the following order of priority:
        - **A.** 1 fragment (ideally 0.5 to 1 gram, or a piece 0.7-1.0 cm in diameter) collected in warm RPMI medium supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin.
        - **B.** 1 fragment placed in a cryovial and frozen in liquid N2.
        - **C.** 1 fragment placed in a vial containing PBS buffered formalin (only one).
    - Normal tissue. As much excess normal tissue as possible will be collected, in the following order of priority:
        - **A.** 1 fragment placed in a cryovial and frozen in liquid N2.
        - **B.** 1 fragment placed in a vial containing PBS buffered formalin (only one).
- Both for tumor and normal tissue as many vials of N2-preserved tissue will be collected.

Tissue Sample Implantation in Mice

Tumor tissues will be implanted in mice following the procedures listed in the protocol ***Generation of a cancer direct xenograft colony with primary and metastatic tumors*** that has been approved by the University of Colorado Institutional Animal Care and Use Committee. Animals are maintained under the American Association of Laboratory Animal Care guidelines. Briefly, after washing several times in media, tumors will be cut into pieces measuring approximately 3-4 mm in diameter while submerged in antibiotic containing medium, dipped in matrigel to explant into mice.

Assessment	Screening	G-CSF mobilization and HSC Harvest (Does not need to be completed prior to Biopsy)								Primary Biopsy & Implantation	Additional/Optional Tumor Biopsies & Blood Collection		
											Cycle 1		≥ Cycle 2
	Day									Any time between consent and next anti-cancer treatment	Day of anti-cancer treatment		
	-14 to -1	1 (Baseline)	2	3	4	5	6 (+/- 1 day)	7 (+/- 1 day)	35 to 42		Prior to treatment start	21 (+/- 2 days)	21 (+/- 2 days)
Informed Consent [1]	X												
Medical History [2]	X												
Physical Exam [3]	X							X(+ 2 days)					
Vital Signs [4]	X												
O2 Saturation	X												
Prior/Concomitant Medication [5]	X												
Baseline Condition Assessment	X	X[18]											
ECOG [6]	X												
CMP (Chemistry) [7]	X							X(+ 2 days)					
CBC [8]	X							X(+ 2 days)					
Tumor Measurements [9]	X									X	X		
Whole Blood for Genomic Testing [10]	X												
G-CSF administration [11]		X	X	X	X								
Blood sample for Circ. B and T cell distrib.										X			
HSC Harvesting [12]							X	X					
Primary tumor biopsy [13]										X			
Optional Consent for Subsequent Blood/Biopsy[14]									X				
Optional Sequential Tumor Biopsy [15]											X	X	
Optional Sequential Blood [16]											X	X	X
Adverse Events [17]		X						X(+ 2 days)	X[17]				
Optional Tissue Collection from SOC [19]										X			
Optional Research Tumor Biopsy										X			

1. Informed Consent will be obtained for study participation.
2. **Medical History:** This will be performed as part of screening evaluation for study participation within 14 days of study initiation.
3. **Physical exam:** This will be performed as part of screening evaluation for study participation within 14 days of study initiation.
4. **Vital Signs to include:** BP (systolic and diastolic), pulse, respiration rate, and body temperature. To be collected within 14 days of study initiation.
5. Prior/Concomitant Medications: Medications and vitamins/supplements that the patient is taking will be reviewed at each time point indicated.
6. **ECOG Performance Status:** Must be 0, 1, or 2 at time of study enrollment.
7. **Chemistry Panel (CMP) includes:** Sodium (Na), Potassium (K), Chloride (Cl), Blood Urea Nitrogen (BUN), Creatinine (Cr), Alkaline Phosphatase (Alk Phos), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Total Protein (TP) and Albumin (Alb).
8. **Complete Blood Count (CBC) includes:** Total white blood cells (WBC), Hemoglobin (Hgb), Platelet Count (Plt), Absolute Neutrophil Count (ANC), volume parameters, formula.
9. **Tumor Response Measurements:**
   - For screening, measureable disease will be determined by standard clinical practice per the investigator.
   - Prior to biopsies, patients will have tumor measurements per standard clinical practice as determined by the provider performing the biopsy.
   - For patients who initiation subsequent treatment regimens, tumor measurements will be conducted as per standard clinical practice for each patient's disease, as determined by their standard of care clinical research team.
   - Response data will be collected from radiological imaging or clinical assessments if determined to be relevant by the Principal Investigator. Data collected will be evaluated using the Response Criteria in Solid Tumors (RECIST) version 1.1, if applicable and relevant.
10. **Whole Blood Sample for Genomic Testing:** 10 mL prior to Day 1 G-CSF administration.
11. **G-CSF Administration:** Patients will receive 10 µg/kg/day G-CSF subcutaneously in a 4-day mobilization schedule
12. **HSC Harvest:** Conducted on days 6 and 7 until a sufficient number of HSC are collected (at least 2 x 10^6) by means of peripheral blood draw of 100 mL per day.
13. Excisional or core biopsy of most accessible lesion. Requires minimum size of 3 mm x 1 mm. Implanted once humanized mice are ready to be implanted (typically 4-8 weeks post HSC infusion into mice).
14. **Optional Subsequent Blood/Biospy Consent:** The patient must sign the *Consent for Optional Subsequent Tumor Biopsies and Blood Collection (if relevant to the main study)* prior to any *additional* samples being collected not stipulated in first consent. Can be collected at other points during study other than screening. Must be performed within 4 weeks of the initiation of Cycle 1 Day 1 of study related treatments.
15. **Optional Sequential Tumor Biopsies:** Samples to be collected once patient starts each new anti-cancer therapy deemed to be of relevance for humanized model. Samples should be collected sequentially prior to C1D1 of therapy, then once more at Day 21 of treatment (+/- 2 days). If no intervening therapy had occurred from the time of the Primary Tumor Biopsy, the pre-treatment biopsy may be waived by the Principal Investigator. Subsequent biopsies can include safely accessible skin lesions, nodes, liver lesions, etc.
16. **Optional Sequential Blood Samples:** Samples to be collected once patient starts each new anti-cancer therapy deemed to be of relevance for humanized model. Samples should be collected sequentially prior to C1D1 of therapy, then every 21 days thereafter (+/- 2 days). This can occur before or after the Primary Tumor Biopsy. If no intervening therapy had occurred from the time of the Primary Tumor Biopsy, the pre-treatment blood sample may be waived by the Principal Investigator.
17. **Adverse Event Assessments:** Adverse events will be assessed in person or over the phone by the PI or sub-investigator. Follow-up AE assessment will occur 30 days post-harvest +/- 2 days (days 35 to 42).
18. **Baseline Condition Assessment:** Repeat at Baseline/Day 1 if not done in prior 14 days
19. **Optional Tissue Collection from SOC**: If the patient consents to optional tissue collection (*Main Consent Form*, "Optional Procedure 2 - Optional Future Tissue Biopsies – Standard of Care"), we will collect excess tissue from any additional scheduled biopsies or resections, as part of his/her regular clinical care for HNSCC or melanoma.
20. **Optional Research Tumor Biopsy**: If the patient signs the *Optional Research Tumor Biopsy (Non-Standard of Care) Consent Form* the patient will have a core biopsy of tumor areas, with radiologic guidance with ultrasound if required.

COMIRB
APPROVED
For Use
14-Jun-2017
13-Jun-2018

Principal Investigator: **Antonio Jimeno, MD**
COMIRB No: **14-0842**
Version Date: **June 1, 2017**

Study Title: Pilot Study of Tissue and Hematopoietic/Mesenchymal Stem Cell Collection for Humanized Xenograft Studies in Melanoma and Squamous Head and Neck Cancer

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You are being asked to be in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Why is this study being done?

This study plans to learn more about melanoma and head and neck squamous cell cancer (HNSCC).

You are being asked to be in this research study because you were diagnosed as having melanoma or HNSCC. We are asking you to agree to let us collect your blood and tumor tissue samples so we can study how your cancer may grow if we put it into mice. This is called *xenograft*. By growing the tumor in the mouse, rather than in a petrie dish, we will be able to learn from a larger and more varied number of samples more quickly. We also refer to this as humanized models. Your samples will be tested in the humanized models to determine individual characteristics of the cancer cells. We will also test anti-cancer drugs. We hope to learn what predicts that a patient will benefit from a treatment and to discover better and more individualized treatments for these cancers.

Other people in this study

Up to 40 people from your area will participate in the study.

What happens if I join this study?

If you join the study, you will be asked to read and sign this consent form. This study has both study related procedures and optional research procedures which will be listed here. Optional parts of this study are not required. You will be given the choice at the end of this section to take part in the optional procedures if you want to.

Before the Study (Screening) Procedures:

- Review your medical history
- A physical exam (check height, weight, vital signs, O2 saturation, etc.)
- Review your current medications

- Laboratory blood tests including complete blood count and comprehensive metabolic panel (check liver and kidney functions, etc.)
- We will draw about 2 teaspoons of blood for germline DNA testing. Germline testing looks at a line or sequence of germ cells that have genetic material that may be passed to a child or may be present in your family. The results of this testing will not be placed in your medical record, given to your doctor or given to you.

During the Study Procedures:

Blood Collections and Blood Booster

- On 4 consecutive days you will be given, or directed how to give yourself, a blood booster called filgrastim so we may obtain peripheral hematopoietic/mesenchymal stems cells (*HSC*). This use of filgrastim is also called granulocyte colony-stimulating (G-CSF). Filgrastim is being used for a purpose that is not currently approved by the FDA.
- You will have one day without injections and blood draws, and then we will collect your blood on two consecutive days, or as soon as your HSC level is sufficient. We will draw a little more than 6 tablespoons of blood each day to collect HSC blood samples.
  - We will also draw 2 teaspoons of blood for standard laboratory tests (including 1 teaspoon each for complete blood count, and comprehensive metabolic panel).
  - We will also ask you questions about your health, how you are feeling and if you are having any side effects.

  In the rare event we do not get enough cells we may repeat the above process a few weeks after the first round.

Primary Tumor Biopsy and Blood Collection. These procedures can be done before the blood collection, at the same time as the HSC blood collection or they can be done later.

- You will have a tumor biopsy.
- We will draw about 2 teaspoons of blood to determine circulating white blood cell distribution. If this procedure is done at the same time as the HSC collection then this will not be a separate procedure.

- If you have previously participated in a xerograph research study collecting tumor tissue with Dr. Jimeno as the principal investigator, we may be able to waive the tumor biopsy portion of the study.

Follow-up. About 30 days after your last HSC blood collection

- We will contact you by phone or in person to ask you questions about your health, how you are feeling, and if you are having any side effects.

Main Study Samples Use:

We will process and use these blood and tumor samples to be implanted into mice and generate cell lines. These cell lines may potentially live forever. We will compare blood and tumor protein, immune and genetic profiles. We will explore various laboratory processes to improve our methods. We will use some of these blood and tumor samples for experiments and comparisons with other patient's samples, since in this project we will acquire samples from 40 patients. We will also keep samples frozen in case we need to repeat the experiments.

We may ask if you would be willing to provide additional blood and tumor tissue samples. Any request for additional samples is optional. You can choose to participate or not. This will be discussed further in the *Optional Study Procedures* section below.

Optional Study Procedures:

Optional parts of this study are voluntary and are not required. You can still participate in the main study if you choose not to take part in the optional study procedures.

Each optional part of the study will be described here. *No matter what you decide to do about these optional parts of the study, you may still take part in the main study.*

Optional Procedure 1

Possible Subsequent Tumor Biopsies and Blood Collection (if relevant to the main study)

We may ask you if you would be willing to provide additional Research Tumor Biopsies and Blood Draws. If your cancer treatment changes, we might request the following additional research samples:

- Blood Samples – every 21 days (for the duration of anti-cancer therapy)
- Tumor Tissue Biopsies
  - Before starting any therapy (at the discretion of the study doctor)
  - 21 days after starting any therapy

You have the **option** of whether or not you want to provide these additional samples. *If we request these additional research samples, you will be given a separate optional consent to read and consider at that time.*

Optional Procedure 2

Optional Future Tissue Biopsies – Standard of Care

It is possible that you may have additional tissue biopsies scheduled as part of your standard medical care. If so, we would like to ask if you would be willing to donate excess tissue from these future procedures.

We would also like to keep a sample of this tissue frozen (cryopreserved) for future research called "banking". Future banking is another optional procedure and you will be asked separately below if you wish to take part in that optional procedure.

Please read the statement below. Check "Yes" or "No", and initial to indicate your choice. If you have any questions, please talk to your doctor or nurse.

Would you be willing to donate excess tissue obtained from any subsequent (additional) biopsies or surgeries as part of your regular clinical care for melanoma or HNSCC?

☐ **Yes** ☐ **No** **_____Initials**

Optional Procedure 3

Optional Future Tissue Biopsies – For Research (Non-Standard of Care)

We may ask if you are willing to provide an additional tumor biopsy. If you are not scheduled for a tissue biopsy as part of your standard medical care, *you may be given a separate optional consent to read and consider at that time*.

Optional Procedure 4

Optional Consent for Data and Specimen Banking for Future Research

Dr. Antonio Jimeno would like to keep some of the data, blood and tissue that is taken during the study but is not used for other tests. If you agree, the data and samples will be kept and may be used in future research to learn more about melanoma and head and neck squamous cell cancer (HNSCC). The research that is done with your data and samples is not designed to specifically help you. It might help people who have melanoma and HNSCC and other diseases in the future. Reports about research done with your data and samples will not be given to you or your doctor. These reports will not be put in your health records. The research using your data and samples will not affect your care.

The choice to let Dr. Antonio Jimeno keep the data and samples for future research is up to you. No matter what you decide to do, it will not affect the care that you will receive as part of the study. If you decide now that your data and samples can be kept for research, you can change your mind at any time and contact your study doctor to let him or her know that you do not want Dr. Antonio Jimeno to use your data and samples any longer, and they will no longer be used for research. Otherwise, they may be kept until they are used up, or until Dr. Antonio Jimeno decides to destroy them.

When your data and samples are given to other researchers in the future, Dr. Antonio Jimeno will not give them your name, address, phone number or any other information that will let the researchers know who you are.

Sometimes data and samples are used for genetic research (about diseases that are passed on in families). Even if your data and samples are used for this kind of research, the results will not be told to you and will not be put in your health records. Your data and samples will only be used for research and will not be sold. The research done with your data and samples may help to develop new products in the future, but there is no plan for you to be paid.

The possible benefits of research from your data and samples include learning more about what causes melanoma and HNSCC and other diseases, how to prevent them and how to treat them. The greatest risk to you is the release of your private information. Dr. Antonio Jimeno will protect your records so that your name, address and phone number will be kept private. The chance that this information will be given to someone else is very small. There will be no cost to you for any data or sample collection and storage by Dr. Antonio Jimeno.

Please read each sentence below and think about your choice. After reading each sentence, circle "yes" or "no." If you have questions, please talk to your doctor or nurse. Remember, no matter what you decide to do about the storage and future use of your data and samples, you may still take part in the study.

I give my permission for my data and tissue to be stored in a central tissue bank at the University of Colorado for future use by the study investigators:

1. I give my permissions for my data, blood and tissue samples to be kept by Dr. Antonio Jimeno for use in future research to learn more about how to prevent, detect, or treat melanoma and HNSCC.

   ☐ Yes ☐ No _____Initials

2. I give my permissions for my data, blood and tissue samples to be used for research about other health problems (for example: causes of heart disease, osteoporosis, diabetes).

   ☐ Yes ☐ No _____Initials

3. I give my permission for my study doctor (or someone he or she chooses) to contact me in the future to ask me to take part in more research.

   ☐ Yes ☐ No _____Initials

If you decide to withdraw your consent for the optional parts, you can continue to take part in the main study, unless you withdraw your consent for the main study as well.

At the end of this consent form, you will also be asked to allow information collected from your optional specimen donations to be used. You need to agree to have information from these optional procedures to be used, or you cannot take part in these optional study procedures.

What are the possible discomforts or risks?

Discomforts you may experience while in this study include:

Risks of taking Filgrastim (G-CSF):

The risks associated with receiving filgrastim for boosting cell production for collection are mild-to-moderate muscle and/or bone pain and mild headache.

Other rare but serious potential risks of filgrastim include:

- Allergic reaction: it has been reported in less than 1 in 4000 administrations
  - skin reaction (rash, itching, facial blisters)
  - wheezing or labored breathing
  - Low blood pressure (hypotension)
  - Rapid heart beating (tachycardia).
    These symptoms generally go away after taking antihistamines, steroids, bronchodilators, and/or epinephrine.

- Splenic rupture has been reported following the administration of filgrastim. If you have pain in your left side of your abdomen you should contact your doctor.
- Acute Respiratory Distress Syndrome. If you develop fever, or labored breathing you should contact your doctor.

Filgrastim has not been studied in pregnant women so if you become pregnant, the particular treatment or procedures involved in the study may involve risks to the embryo or fetus which are currently unclear. ***While participating in this research study, you should not become pregnant, father a baby, or nurse a baby. Let your research doctor know immediately if you become pregnant or find out that you are going to be the father of a child.*** Talk to your doctor about ways to prevent pregnancy.

Risks of Having Blood Taken

At different points during this study we will need to get about 10 tablespoons of blood from you. We will get blood by putting a needle into one of your veins and letting the blood flow into a glass tube. You may feel some pain when the needle goes into your vein. A day or two later, you may have a small bruise where the needle went under the skin.

Risk of Having a Tumor Biopsy

In this study we will need to have one or more small sample(s) of your tumor. This procedure is called a "biopsy." Before we take the sample(s), we will give you some medicine to numb the area. We will then make a small cut in your skin and take the sample(s) by pressing a hollow needle into your tumor tissue. When we take the needle out, it will remove a small circle of your tumor tissue called a "plug."

There are some risks to taking a sample of tumor tissue in this way. There is a small chance that taking a sample of tumor tissue this way could cause an infection where the needles go in. You could also have an allergic reaction to the numbing medicine. But this is rare. After your skin heals up, you may have a small scar where we took the sample.

Risk of Loss of Confidentiality

There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

Other possible risks include:

If you become pregnant, the particular treatment or procedures involved in the study may involve risks to the embryo or fetus which are currently unclear.

The study may include risks that are unknown at this time.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about melanoma and HNSCC.

This study is not designed to treat any illness or to improve your health. Also, there may be risks, as discussed in the section describing the discomforts or risks.

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Who is paying for this study?

This research is being sponsored by the University of Colorado the National Institutes of Health and the National Cancer Institute.

Financial Disclosure

Dr. Gonzalez, one of the study doctors involved with this clinical trial, is on the advisory board for the study drug manufacturer in the past 12 months. Please feel free to ask any further questions you might have about this matter.

Will I be paid for being in the study?

You will not be paid to be in the study.

You may be eligible for travel, meal and/or lodging reimbursement. Talk to the study team for more information.

Will I have to pay for anything?

It will not cost you anything to be in the study.

The University of Colorado will pay for all study procedures as well as filgrastim and any medication used for the research tumor biopsy you will get in this study. You will not have to pay for any medical care that is part of this study.

Is my participation voluntary?

You do not have to be in this study if you do not want to be. Even if you decide to be in this study, you can change your mind and stop at any time. If we learn new information that might make you want to leave this study, we will tell you about it.

If you leave this study, you will not lose any of the benefits that you would normally get outside of this study. Leaving this study will not affect your employment status or your reputation. Leaving this study will not change your ability to get government assistance. If you leave this study, the only benefits that you will lose are the ones you are getting as part of this study.

Can I be removed from this study?

You may be taken out of this study if the study doctor thinks it is not safe for you to be in the study. You can be taken out of the study even if you do not want to leave the study.

If you are taken out of this study, you will not lose any of the benefits that you would normally get outside of the study. Being taken out of the study will not affect your employment status or your reputation. Being taken out of the study will not change your ability to get government assistance. If you are taken out of the study, the only benefits you will lose are the ones you are getting as part of this study.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should call Dr. Antonio Jimeno immediately. His phone number is 720-848-1543 or 720-848-0000 (24 hour contact number, ask for the medical oncology fellow on-call).

We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Who do I call if I have questions?

The researcher carrying out this study is Dr. Antonio Jimeno. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. Antonio Jimeno at 720-848-1543. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. Antonio Jimeno with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

Who will see my research information?

The University of Colorado Denver (UCD) and its affiliated hospital(s) have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver
- University of Colorado Hospital

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Antonio Jimeno, MD, PhD
University of Colorado Denver
University of Colorado Cancer Center
P.O. Box 6511
Campus Box 8117
Aurora, Colorado 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB)
- The study doctor and the rest of the study team.
- The University of Colorado School, the entity who is paying for this research study.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator. Some of the research procedures involve genetic testing or the use of your genetic information. Your genetic information will not be released to others.

Information about you that will be seen, collected, used and disclosed in this study:

- Name and Demographic Information (age, sex, ethnicity, address, phone number, etc.).
- Your social security number
- Portions of your previous and current Medical Records that are relevant to this study, including but not limited to Diagnosis(es), History and Physical, laboratory or tissue studies, radiology studies, procedure results
- Research Visit and Research Test records
- Blood and Tissue samples and the data with the samples.
- Billing or financial information

What happens to Data, Tissue, Blood and Specimens that are collected in this study?

Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data, tissue, blood and specimens collected from you during this study are important to this study and to future research. If you join this study:

- The data, tissue, blood, or other specimens given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data, tissue, blood, or other specimens collected from you.
- If data, tissue, blood, or other specimens are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

HIPAA Authorization for Optional Additional Study Procedures

In this form, you were given the option to agree to additional, optional research procedures. You must also give us your permission, under HIPAA rules, to use and disclose the information collected from these optional procedures, as described above.

Some of these optional procedures may involve genetic testing or the use of your genetic information. Your genetic information will not be released to others.

If you decline to give us permission to use and disclose your information, you cannot take part in these optional procedures, but you can still participate in the main study. Please initial next to your choice:

_____ I give permission for my information, from the optional procedures I have agreed to above, to be used and disclosed as described in this section.

_____ I **do not** give permission for my information for any optional procedures to be used and disclosed; I understand that I will not participate in any optional procedures.

Agreement to be in this study and use my data

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I will get a signed and dated copy of this consent form.

Signature: _____ Date: _____

Print Name: _____

Consent form explained by: _____ Date: _____

Print Name: _____

Investigator: _____ Date: _____
Investigator must sign within 30 days

If applicable, the signature line for witness below is required for consent of non-reading subjects, decisionally challenged adults, or consent using a short form.

Signature: _____ Date: _____

Print Name: _____

Witness of Signature ☐

Witness of consent process ☐

COMIRB
APPROVED
For Use
14-Jun-2017
13-Jun-2018

Consent for Optional Subsequent Tumor Biopsies and Blood Collection (if relevant to the main study)

Principal Investigator: **Antonio Jimeno, MD**
COMIRB No: **14-0842**
Version Date: **June 1, 2017**

Study Title: Pilot Study of Tissue and Hematopoietic/Mesenchymal Stem Cell Collection for Humanized Xenograft Studies in Melanoma and Squamous Head and Neck Cancer

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You are being asked to be in an optional research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Why is this study being done?

You are being asked to be in this optional research study because:

1. You signed the main Informed Consent and Authorization Form and are taking part in the main part of this study.

and

2. You have started a new anti-cancer therapy as part of your regular clinical care for melanoma or head and neck squamous cell cancer (HNSCC) that is relevant to the main part of this study.

This optional study plans to learn more about melanoma and head and HNSCC. We are asking if you would be willing to provide research tumor biopsies and blood donations as another part of the research being conducted with this study. We want to analyze the additional research samples collected after you started a new therapy that is relevant to the main study.

The testing we will do on this tissue is the same as the testing done on the original sample you provided us. That testing may include putting the tissue in mice (humanized model) to compare the samples, and to study the protein and genetic profiles of different tumor cells.

Other people in this study

Up to 40 people from your area will participate in the study.

What happens if I join this study?

If you join the study, you will be asked to read and sign this consent form before study procedures would begin.

We will collect the following research samples relevant to the main study:

- Blood Samples – every 21 days (for the duration of anti-cancer therapy)
- Tumor Tissue Biopsies
  - Before starting any therapy
  - 21 days after starting any therapy

If you agree to participate in this study, information about your diagnosis, medical history, disease, and treatment will also be collected. This information will be linked to your tumor tissue so the study doctors have a better understanding of how these tests affect patient outcome.

Your sample will only be used for research and will not be sold. However, the research done with your samples, derivatives or extracts may help to develop new products or ideas in the future. There is no plan for you to share in any financial gains.

We would also like to keep a sample of tissue from your tumor frozen (cryopreserved) for future research called "banking". Future banking is another optional procedure and you will be asked below if you want to participate in this optional part of this study.

Optional Consent for Data and Specimen Banking for Future Research

Dr. Antonio Jimeno would like to keep some of the data, blood and tissue that is taken during the study but is not used for other tests. If you agree, the data and samples will be kept and may be used in future research to learn more about melanoma and head and neck squamous cell cancer (HNSCC). The research that is done with your data and samples is not designed to specifically help you. It might help people who have melanoma and HNSCC and other diseases in the future. Reports about research done with your data and samples will not be given to you or your doctor. These reports will not be put in your health records. The research using your data and samples will not affect your care.

The choice to let Dr. Antonio Jimeno keep the data and samples for future research is up to you. No matter what you decide to do, it will not affect the care that you will receive as part of the study. If you decide now that your data and samples can be kept for research, you can change your mind at any time and contact your study doctor to let him or her know that you do not want Dr. Antonio Jimeno to use your data and samples any longer, and they will no longer be used

for research. Otherwise, they may be kept until they are used up, or until Dr. Antonio Jimeno decides to destroy them.

When your data and samples are given to other researchers in the future, Dr. Antonio Jimeno will not give them your name, address, phone number or any other information that will let the researchers know who you are.

Sometimes data and samples are used for genetic research (about diseases that are passed on in families). Even if your data and samples are used for this kind of research, the results will not be told to you and will not be put in your health records. Your data and samples will only be used for research and will not be sold. The research done with your data and samples may help to develop new products in the future, but there is no plan for you to be paid.

The possible benefits of research from your data and samples include learning more about what causes melanoma and HNSCC and other diseases, how to prevent them and how to treat them. The greatest risk to you is the release of your private information. Dr. Antonio Jimeno will protect your records so that your name, address and phone number will be kept private. The chance that this information will be given to someone else is very small. There will be no cost to you for any data or sample collection and storage by Dr. Antonio Jimeno.

Please read each sentence below and think about your choice. After reading each sentence, circle “yes” or “no.” If you have questions, please talk to your doctor or nurse. Remember, no matter what you decide to do about the storage and future use of your data and samples, you may still take part in the study.

I give my permission for my data and tissue to be stored in a central tissue bank at the University of Colorado for future use by the study investigators:

1. I give my permissions for my data, blood and tissue samples to be kept by Dr. Antonio Jimeno for use in future research to learn more about how to prevent, detect, or treat melanoma and HNSCC.

   ☐ Yes ☐ No _____Initials

2. I give my permissions for my data, blood and tissue samples to be used for research about other health problems (for example: causes of heart disease, osteoporosis, diabetes).

   ☐ Yes ☐ No _____Initials

3. I give my permission for my study doctor (or someone he or she chooses) to contact me in the future to ask me to take part in more research.

   ☐ Yes ☐ No _____Initials

If you decide to withdraw your consent for the optional parts, you can continue to take part in the main part of this study, unless you withdraw your consent for the main part of the study as well.

At the end of this consent form, you will also be asked to allow information collected from your optional specimen donations to be used. You need to agree to have information from these optional procedures to be used, or you cannot take part in these optional study procedures.

What are the possible discomforts or risks?

Discomforts you may experience while in this study include:

Risks of Having Blood Taken

At different points during this study we will need to get about 2 teaspoon of blood from you. We will get blood by putting a needle into one of your veins and letting the blood flow into a glass tube. You may feel some pain when the needle goes into your vein. A day or two later, you may have a small bruise where the needle went under the skin.

Risk of Having a Tumor Biopsy

In this study we will need to have one or more small sample(s) of your tumor. This procedure is called a "biopsy." Before we take the sample(s), we will give you some medicine to numb the area. We will then make a small cut in your skin and take the sample(s) by pressing a hollow needle into your tumor tissue. When we take the needle out, it will remove a small circle of your tumor tissue called a "plug."

There are some risks to taking a sample of tumor tissue in this way. There is a small chance that taking a sample of tumor tissue this way could cause an infection where the needles go in. You could also have an allergic reaction to the numbing medicine. But this is rare. After your skin heals up, you may have a small scar where we took the sample.

Risk of Loss of Confidentiality

There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it can not be guaranteed.

Other possible risks include:

If you become pregnant, the particular treatment or procedures involved in the study may involve risks to the embryo or fetus which are currently unclear.

The study may include risks that are unknown at this time.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about melanoma and HNSCC.

This study is not designed to treat any illness or to improve your health. Also, there may be risks, as discussed in the section describing the discomforts or risks.

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Who is paying for this study?

This research is being sponsored by the University of Colorado, National Institutes of Health and National Cancer Institute.

Will I be paid for being in the study?

You will not be paid to be in the study.

You may be eligible for travel, meal and/or lodging reimbursement. Talk to the study team for more information.

Will I have to pay for anything?

It will not cost you anything to be in the study.

The University of Colorado will pay for all treatments and medicines you will get in this study. You will not have to pay for any medical care that is part of this study.

Is my participation voluntary?

You do not have to be in this study if you do not want to be. Even if you decide to be in this study, you can change your mind and stop at any time. If we learn new information that might make you want to leave this study, we will tell you about it.

If you leave this study, you will not lose any of the benefits that you would normally get outside of this study. Leaving this study will not affect your employment status or your reputation. Leaving this study will not change your ability to get government assistance. If you leave this study, the only benefits that you will lose are the ones you are getting as part of this study.

Can I be removed from this study?

You may be taken out of this study if the study doctor thinks it is not safe for you to be in the study. You can be taken out of the study even if you do not want to leave the study. Also, the University of Colorado can decide to stop the study at any time.

If you are taken out of this study, you will not lose any of the benefits that you would normally get outside of the study. Being taken out of the study will not affect your employment status or your reputation. Being taken out of the study will not change your ability to get government assistance. If you are taken out of the study, the only benefits you will lose are the ones you are getting as part of this study.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should call Dr. Antonio Jimeno immediately. His phone number is 720-848-1543 or 720-848-0000 (24 hour contact number, ask for the medical oncology fellow on-call).

We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Who do I call if I have questions?

The researcher carrying out this study is Dr. Antonio Jimeno. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. Antonio Jimeno at 720-848-1543. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. Antonio Jimeno with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

Who will see my research information?

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The institutions involved in this study include:

- University of Colorado Denver
- University of Colorado Hospital

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Antonio Jimeno, MD, PhD
University of Colorado Denver

University of Colorado Cancer Center
P.O. Box 6511
Campus Box 8117
Aurora, Colorado 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB)
- The study doctor and the rest of the study team.
- The University of Colorado, the entity who is paying for this research study.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator.

Some of the research procedures involve genetic testing or the use of your genetic information. Your genetic information will not be released to others.

Information about you that will be seen, collected, used and disclosed in this study:

- Name and Demographic Information (age, sex, ethnicity, address, phone number, etc.).
- Your social security number
- Portions of your previous and current Medical Records that are relevant to this study, including but not limited to Diagnosis(es), History and Physical, laboratory or tissue studies, radiology studies, procedure results
- Research Visit and Research Test records
- Blood and Tissue samples and the data with the samples.
- Billing or financial information

What happens to Data, Tissue, Blood and Specimens that are collected in this study?

Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data, tissue, blood and specimens collected from you during this study are important to this study and to future research. If you join this study:

- The data, tissue, blood, or other specimens given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data, tissue, blood, or other specimens collected from you.
- If data, tissue, blood, or other specimens are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

HIPAA Authorization for Optional Additional Study Procedures

In this form, you were given the option to agree to additional, optional research procedures. You must also give us your permission, under HIPAA rules, to use and disclose the information collected from these optional procedures, as described above.

Some of these optional procedures may involve genetic testing or the use of your genetic information. Your genetic information will not be released to others.

If you decline to give us permission to use and disclose your information, you cannot take part in these optional procedures, but you can still participate in the main study. Please initial next to your choice:

_____ I give permission for my information, from the optional procedures I have agreed to above, to be used and disclosed as described in this section.

_____ I **do not** give permission for my information for any optional procedures to be used and disclosed; I understand that I will not participate in any optional procedures.

Agreement to be in this study and use my data

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I will get a signed and dated copy of this consent form.

Signature: _____ Date: _____

Print Name: _____

Consent form explained by: _____ Date: _____

Print Name: _____

Investigator: _____ Date: _____
Investigator must sign within 30 days

If applicable, the signature line for witness below is required for consent of non-reading subjects, decisionally challenged adults, or consent using a short form.

Signature: _____ Date: _____

Print Name: _____

Witness of Signature ☐

Witness of consent process ☐

COMIRB
APPROVED
For Use
14-Jun-2017
13-Jun-2018

Optional Research Tumor Biopsy (Non-Standard of Care) Consent Form

Principal Investigator: **Antonio Jimeno, MD**
COMIRB No: **14-0842**
Version Date: **June 1, 2017**

Study Title: Pilot Study of Tissue and Hematopoietic/Mesenchymal Stem Cell Collection for Humanized Xenograft Studies in Melanoma and Squamous Head and Neck Cancer

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You are being asked to be in an optional research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Why is this study being done?

You are being asked to be in this optional research study because:

1. You signed the main Informed Consent and Authorization Form and are taking part in the main part of this study.

and

2. You are NOT scheduled for any additional biopsies or resections as part of your regular clinical care for melanoma or HNSCC.

This optional study plans to learn more about melanoma and head and neck squamous cell cancer (HNSCC). The testing we will do on this tissue is the same as the testing done on the original sample you provided us. That testing may include putting the tissue in mice (humanized model) to compare the samples, and to study the protein and genetic profiles of different tumor cells.

Other people in this study

Up to 40 people will participate in this study.

What happens if I join this study?

If you join the study, you will be asked to sign and date this consent form before study procedures would begin.

Study Procedures:

1. Tumor Biopsy: You will be asked to have a biopsy of your tumor. This biopsy will be done when it is feasible and safe to do so. This tumor tissue will be collected and stored at the University of Colorado until it is analyzed.
2. Tissue Use for Research. We will use some of the tumor tissue that is collected for research studies as soon as the sample arrives in the laboratory.

This study may include germline or genetic testing.

- Germline testing looks at a line or sequence of germ cells that have genetic material that may be passed to a child or may be present in your family. The results of this testing will not be placed in your medical record, given to your doctor or given to you.
- Genetic Testing allows the genetic diagnosis of vulnerabilities to inherited diseases, such as cancer. The results of this testing will not be placed in your medical record, given to your doctor or given to you.

If you agree to participate in this study, information about your diagnosis, medical history, disease, and treatment will also be collected. This information will be linked to your tumor tissue so the study doctors have a better understanding of how these tests affect patient outcome.

Your sample will only be used for research and will not be sold. However, the research done with your samples, derivatives or extracts may help to develop new products or ideas in the future. There is no plan for you to share in any financial gains.

We would also like to keep a sample of tissue from your tumor frozen (cryopreserved) for future research called "banking". Future banking is another optional procedure and you will be asked below if you want to participate in this optional part of this study.

Optional Procedure:

Optional Consent for Data and Specimen Banking for Future Research

Dr. Antonio Jimeno would like to keep some of the data and tissue that is taken during the study but is not used for other tests. If you agree, the data and samples will be kept and may be used in future research to learn more about melanoma and head and neck squamous cell cancer (HNSCC). The research that is done with your data and samples is not designed to specifically help you. It might help people who have melanoma and HNSCC and other diseases in the future. Reports about research done with your data and samples will not be given to you or your doctor. These reports will not be put in your health records. The research using your data and samples will not affect your care.

The choice to let Dr. Antonio Jimeno keep the data and samples for future research is up to you. No matter what you decide to do, it will not affect the care that you will receive as part of the study. If you decide now that your data and samples can be kept for research, you can change your mind at any time and contact your study doctor to let him or her know that you do not want Dr. Antonio Jimeno to use your data and samples any longer, and they will no longer be used for research. Otherwise, they may be kept until they are used up, or until Dr. Antonio Jimeno decides to destroy them.

When your data and samples are given to other researchers in the future, Dr. Antonio Jimeno will not give them your name, address, phone number or any other information that will let the researchers know who you are.

Sometimes data and samples are used for genetic research (about diseases that are passed on in families). Even if your data and samples are used for this kind of research, the results will not be told to you and will not be put in your health records. Your data and samples will only be used for research and will not be sold. The research done with your data and samples may help to develop new products in the future, but there is no plan for you to be paid.

The possible benefits of research from your data and samples include learning more about what causes melanoma and HNSCC and other diseases, how to prevent them and how to treat them. The greatest risk to you is the release of your private information. Dr. Antonio Jimeno will protect your records so that your name, address and phone number will be kept private. The chance that this information will be given to someone else is very small. There will be no cost to you for any data or sample collection and storage by Dr. Antonio Jimeno.

Please read each sentence below and think about your choice. After reading each sentence, circle “yes” or “no.” If you have questions, please talk to your doctor or nurse. Remember, no matter what you decide to do about the storage and future use of your data and samples, you may still take part in the study.

I give my permission for my data and tissue to be stored in a central tissue bank at the University of Colorado for future use by the study investigators:

1. I give my permissions for my data and tissue samples to be kept by Dr. Antonio Jimeno for use in future research to learn more about how to prevent, detect, or treat melanoma and HNSCC.

   ☐ Yes ☐ No _____Initials

2. I give my permissions for my data and tissue samples to be used for research about other health problems (for example: causes of heart disease, osteoporosis, diabetes).

   ☐ Yes ☐ No _____Initials

3. I give my permission for my study doctor (or someone he or she chooses) to contact me in the future to ask me to take part in more research.

   ☐ Yes ☐ No _____Initials

If you decide to withdraw your consent for the optional parts, you can continue to take part in the main part of this study, unless you withdraw your consent for the main part of the study as well.

At the end of this consent form, you will also be asked to allow information collected from your optional specimen donations to be used. You need to agree to have information from these optional procedures to be used, or you cannot take part in these optional study procedures.

What are the possible discomforts or risks?

Discomforts you may experience while in this study include:

Risks of Having a Tumor Tissue Biopsy:

In this study we will need to have one or more small sample(s) of your tumor. This procedure is called a "biopsy." Before we take the sample(s), we will give you some medicine to numb the area. We will then make a small cut in your skin and take the sample(s) by pressing a hollow needle into your tumor tissue. When we take the needle out, it will remove a small circle of your tumor tissue called a "plug."

There are some risks to taking a sample of tumor tissue in this way. There is a small chance that taking a sample of tumor tissue this way could cause an infection where the needles go in. You could also have an allergic reaction to the numbing medicine. But this is rare. After your skin heals up, you may have a small scar where we took the sample.

Risk of Loss of Confidentiality

There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

Other possible risks include:

The study may include risks that are unknown at this time.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about melanoma and HNSCC.

This study is not designed to treat any illness or to improve your health. Also, there may be risks, as discussed in the section describing the discomforts or risks.

Who is paying for this study?

This research is being sponsored by the University of Colorado, the National Institutes of Health and the National Cancer Institutes.

Will I be paid for being in the study?

You will not be paid to be in the study.

You may be eligible for travel, meal and/or lodging reimbursement. Talk to the study team for more information.

Will I have to pay for anything?

The University of Colorado will pay for all treatments and medicines you will get in this study. You will not have to pay for any medical care that is part of this study.

Is my participation voluntary?

You do not have to be in this study if you do not want to be. Even if you decide to be in this study, you can change your mind and stop at any time. If we learn new information that might make you want to leave this study, we will tell you about it.

If you leave this study, you will not lose any of the benefits that you would normally get outside of this study. Leaving this study will not affect your employment status or your reputation. Leaving this study will not change your ability to get government assistance. If you leave this study, the only benefits that you will lose are the ones you are getting as part of this study.

Can I be removed from this study?

You may be taken out of this study if the study doctor thinks it is not safe for you to be in the study. You can be taken out of the study even if you do not want to leave the study. Also, the University of Colorado can decide to stop the study at any time.

If you are taken out of this study, you will not lose any of the benefits that you would normally get outside of the study. Being taken out of the study will not affect your employment status or your reputation. Being taken out of the study will not change your ability to get government assistance. If you are taken out of the study, the only benefits you will lose are the ones you are getting as part of this study.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should call Dr. Antonio Jimeno immediately. His phone number is 720-848-1543 or 720-848-0000 (24 hour contact number, ask for the medical oncology fellow on-call).

We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Who do I call if I have questions?

The researcher carrying out this study is Dr. Antonio Jimeno. You may ask any questions you have now. If you have questions later, you may call Dr. Antonio Jimeno at 720-848-1543. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. Antonio Jimeno with questions. You can also call the Colorado Multiple Institutional Review Board (COMIRB). You can call them at (303) 724-1055.

Who will see my research information?

The University of Colorado Denver (UCD) and its affiliated hospital(s) have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver
- University of Colorado Hospital

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Antonio Jimeno, MD, PhD
University of Colorado Denver
University of Colorado Cancer Center
P.O. Box 6511
Campus Box 8117
Aurora, Colorado 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB)
- The study doctor and the rest of the study team.
- The University of Colorado, the entity who is paying for this research study.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

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Signature: _____ Date: _____

Print Name: _____

Consent form explained by: _____ Date: _____

Print Name: _____

Investigator: _____ Date: _____
Investigator must sign within 30 days

If applicable, the signature line for witness below is required for consent of non-reading subjects, decisionally challenged adults, or consent using a short form.

Signature: _____ Date: _____

Print Name: _____

Witness of Signature ☐

Witness of consent process ☐