CEDARS-SINAI MEDICAL CENTER

CONSENT FORM FOR RESEARCH

TITLE: K5-C200: An Exploratory, Phase II, Open Label, Single-Center, Non-Randomized Study Of [F-18] RGD-K5 Positron Emission Tomography (PET) In Participants With Carotid Artery Stenosis

STUDY SUPPORT PROVIDED BY: NHLBI-NIH (National Institutes of Health)

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AFTER HOURS CONTACT (24 HOURS): (310) 423-3300

This research study is sponsored by the NIH as part of a grant provided to Dr. Tamarappoo as Principal investigator. NIH only reimburses Cedars-Sinai Medical Center for the costs associated with running the study. The NIH is not providing additional compensation to Cedars Sinai Medical Center or the Principal Investigator for their participation in the study.

1. WHAT IS THE PURPOSE OF THIS RESEARCH STUDY?

We are doing this study to examine a new investigational agent compound [F- 18] labeled RGD-K5. This agent will be used to help identify areas of plaque in your carotid arteries that may be "unstable" or at risk of breaking loose. This atherosclerotic plaque (a disease of the arteries characterized by the deposition of plaques of fatty material on their inner walls) in the carotid artery (major blood vessels in the neck that supply blood to the brain, neck, and face) of subjects being considered for carotid revascularization [endarterectomy (CEA, i.e. surgical repair of a blocked Carotid artery) or stenting of your carotid artery (procedure where a **stent** is deployed within the lumen of the **carotid** artery to treat narrowing)]. We want to know if this new agent can detect regions of unstable atherosclerotic plaque in the carotid artery.

You are being asked to participate in this research study because you have carotid artery stenosis (narrowing of your artery due to plaque buildup) and you may undergo a carotid endarterectomy (CEA) or stenting of your carotid artery.

The study may enroll up to 6 people in total at Cedars-Sinai.
This research study is designed to test the investigational use of compound [F- 18] labeled RGD-K5. This drug has not been approved by the U.S. Food and Drug Administration (FDA).

In this study, we want to learn what effects, good or bad, of compound [F- 18] labeled RGD-K5 has on people with your condition. We will give the compound [F- 18] labeled RGD-K5 during the research PET/MRI scans to research participants, assess whether it can detect regions of unstable atherosclerotic plaque in the carotid artery and watch carefully for any side effects.

2. WHAT WILL HAPPEN DURING THE STUDY?

This section provides a general overview of what will happen during your participation in this study. Information included below should be considered along with the flowchart of procedures attached as Appendix A.

The flowchart shows a timeline for research-related or standard of care procedures that are involved in your participation in this study. **Research-related procedures** are those performed solely for the research. They would not be performed if you did not take part in the study. **Standard of care (routine)** procedures would be performed both as part of this study and if you do not participate in this study.

A table describing common medical procedures done solely for the purposes of monitoring and assessing your condition during this study is attached as Appendix B to the end of this consent form. Standard of care procedures that will be repeated or done at greater frequency are listed in the flow chart, attached Appendix A.

Overview of study:

Visit	What procedures/tests that will be done at this visit?	What will need to be brought and/or done for this visit?
Baseline Visit 1 (May happen in your doctor's office or hospital and may be combined with Visit 2)	• Informed Consent reviewed and signed* * *Must occur 1st, prior to any other research activities* • Medical History reviewed Eligibility Labs, if needed	• The purpose of this visit will be to gather information to ensure you qualify for the study
Visit 2 – PET Scans	• Vital Signs obtained (2) • Physical exam • ECG obtained (1) • Blood drawn, if needed • Pregnancy test, if applicable • IV (intravenous) line inserted • A dose of [F-18]RGD-K5 will be given through the IV • PET imaging	• Bring list of medications. • You will be asked how you are feeling during your visit

Follow up Phone call	• Phone call day after PET scans	• List of medications taken since PET scans • You will be asked how you have felt since your PET/CT Scans.
Visit 3 - Day of Surgery	• After the surgeons complete the surgery to remove the plaque in your carotid artery, a portion of the removed plaque will be collected for this research.	• Please notify us if your surgery is rescheduled or cancelled.

Research PET/MRI Imaging of the Carotid Arteries: 2 hours (+/- 30 minutes) after receiving the dose of [F-18] RGD-K5, PET/MRI imaging of your neck (carotid arteries) will be performed. You will be lying on your back with a head fixation device supporting your head to prevent you from moving your head while the images are taken. This scan will take about 30-45min minutes. You will be permitted to get up and move around between injection of the PET agent and testing. You will be asked to drink a glass of water before receiving the dose of [F-18] RGD-K5.

How long will you be in the study:

You will be asked to come to the site approximately for 1 to 2 visits. The day of your scans you will have a PET/MRI it will last approximately 2 ½ to 4 hours. You will be contacted by phone the day after the PET/MRI scans for follow up. On the day that you return for your scheduled surgery, a portion of the tissue samples from the plaque that is removed by your surgeons will be picked up and sent to the lab for this research study. It is expected that your participation in the study will be less than 2 weeks.

3. WHAT ARE THE POSSIBLE RISKS?

Risks of common medical procedures performed solely for research purposes are described in a table attached to the end of this consent form as Appendix B. Side effects and risks of standard of care procedures are not described in this consent form.

This section describes the possible risks and/or discomforts we anticipate you could experience that are related to the study procedures:

Unknown Risks
There may be risks or side effects related to the study drug that are unknown at this time. Many side effects may go away shortly after the study medication or procedure is stopped. However, in some cases they can be serious, long-lasting, permanent, and/or fatal. You will be notified of any significant new findings that become known that may affect your willingness to continue in the study.

Risks Associated with [F-18] RGD-K5:
Based upon the information from a prior study of 5 subjects, the administration of a single dose of the study medication ([F-18] RGD-K5) presented no risks in humans and no adverse events were reported. The results of studies in human for compounds that were similar in structure to RDG-K5, reported no adverse events.

Radiation Risk:
This research study involves exposure to radiation from the RGDK5-PET/MRI scan. This radiation exposure is not necessary for your medical care and is for research purposes only. The total amount of radiation exposure you will receive is equivalent to a uniform whole body exposure of 0.8 rem. This amount is comparable to 16% of the maximum annual exposure for radiation workers (5 rem) allowed by the Nuclear Regulatory Commission. This use involves minimal risk and is necessary for the research information desired.

Pregnant women, fertile females:
Pregnancy tests will be performed on all women of child-bearing potential before enrolling in the study. If the test is positive, you will not be permitted to participate in this study.

Reproductive and Lactation Risks
Taking part in this research study can affect an unborn baby. Therefore, you should not become pregnant or father a baby while on this study. If you or your partner is capable of becoming pregnant you will need to use birth control. Check with the researcher about approved birth control methods to use while participating in this study.

Women should not breastfeed a baby while on this study.

Unknown Risks to the Developing Embryo or Fetus (an unborn baby)
If you are pregnant, or become pregnant during participation in this research, the study drug, procedures and radiation might involve risks to an embryo or fetus, which are currently unknown. It is important that you contact the researcher immediately if you believe you might be pregnant.

MRI Related Risks:
The physical procedure of MRI and administration of intravenous contrast are generally considered low-risk in patients without significant renal dysfunction and other contraindications to intravenous contrast. Since we will exclude patients with significantly elevated creatinine, the risk of renal dysfunction is minimal.

Contrast- We will use Gadovist® which is a gadolinium-based contrast agent routinely used in clinical magnetic resonance imaging. When injected into the body, gadolinium contrast medium makes certain tissues, abnormalities or disease processes more clearly visible on a magnetic resonance imaging scan. They are used to improve the clarity of the scanned images or pictures of the body's internal structures.

Gadolinium contrast medium is given by intravenous injection.
The risk of gadolinium contrast is minimal in patients without severe renal disease.

The most common adverse effects of gadolinium agents (such as Gadovist®) are:

Common, some may be serious (occurs in greater than 20% of people)	**Occasional, some may be serious** (occurs in 4-20% of people)	**Possible, some may be serious** (occurs in 1-3% of people)	**Rare, and serious** (occurs in less than 1% of people)
• None	• Itching of the skin (5%) • Headache (4%) • Nausea (4%)	• Very small risk of local pain • Hypersensitivity (allergic reaction)	• low blood pressure and lightheadedness. This can be treated immediately with IV fluids.

More serious allergic reactions that are life threatening are rare. Gadolinium is not safe for people with late stage kidney disease or who have had a liver transplant. Gadolinium-based contrast agents increase the risk for a rare, but serious adverse reaction, called nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Patients with kidney disease are at increased risk of developing NSF. NSF may cause skin thickening, joint pain and/or swelling, causing feelings of burning, itching and pain that can be severe. In very rare cases, NSF can lead to lung and heart problems and may be life threatening. Participants will have a blood test to measure kidney function and if the blood test is abnormal, they will not be permitted to receive gadolinium.
There is a very small risk of mild headache and local pain. Rarely (<1% of the time) it can cause low blood pressure and lightheadedness. This can be treated immediately with IV fluids. More serious allergic reactions that are life threatening are rare. Gadolinium is not safe for people with late stage kidney disease or who have had a liver transplant.
As with all research procedures and administration of study drugs, subjects will be monitored at all times.

Risks Associated with Contrast Agents: The U.S. Food and Drug Administration (FDA) is investigating the risk of brain deposits following repeated use of gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging (MRI). MRIs help detect abnormalities of body organs, blood vessels, and other tissues. Recent publications in the medical literature have reported that deposits of GBCAs remain in the brains of some patients who undergo four or more contrast MRI scans, long after the last administration. It is unknown whether these gadolinium deposits are harmful or can lead to adverse health effects. FDA, including its National Center for Toxicological Research (NCTR), will study this possible safety risk further. The FDA is working with the research community and industry to understand the mechanism of gadolinium retention and to determine if there are any potential adverse health effects. To reduce the potential for gadolinium accumulation, FDA has cautioned health care professionals to consider limiting GBCA use to clinical circumstances in which the additional information provided by the contrast is necessary. Health care professionals are also urged to reassess the necessity of repetitive GBCA MRIs in established treatment protocols. Healthy control participants should understand your exposure to GBCAs is not clinically indicated.

Incidental Findings and Duplicate Tests
The procedures in this study are for research purposes and no clinical care or information will be provided to you as part of this study. It is possible that the study procedures could detect a medical problem that was not the focus of the research and about which you may not already be aware. If we learn that the results of research procedures could suggest information relevant in an important way to your health, we will notify you. We will not provide any specific diagnosis about the information seen during research scans performed at the Research Imaging Core facility, although we may suggest your

physician order a particular test or procedure to further investigate the finding. Your primary care physician will determine if it is in your best interest to obtain this test for you. There may be added risks of having further diagnostic tests, and we suggest that you discuss this with your primary care physician.

You will not be provided with information from the screening blood test to check your kidney function other than noting whether your screen met our standards. If not, you will be told and encouraged to discuss this with your primary physician. We will not provide the blood test results to your primary physician.

4. ARE THERE BENEFITS IN TAKING PART IN THE STUDY?

If you agree to take part in this research study, there may or may not be direct medical benefit to you. The possible benefits of taking part in the research study are: it will allow the study doctor to know the entire extent of the carotid plaque, plaque composition and will inform them of the anatomy of the carotid artery. Furthermore, if a high inflammatory signal is noted in the carotid artery, there will be a greater degree of monitoring from the doctors. However, no benefit is guaranteed. It is possible that your condition may remain unchanged or even get worse.

The knowledge to be gained from this research may be beneficial for other patients, society or science.

5. WHY WOULD MY PARTICIPATION BE STOPPED?

Your participation in this study may be stopped at any time by the researcher or the sponsor without your consent for any reason, including:

- The study is stopped or suspended;
- Funding for the study is reduced, stopped or withdrawn;
- If it is in your best interest;
- You do not consent to continue in the study after being told of changes in the research that may affect you;
- You do not follow the study procedures.

6. ARE THERE ANY OTHER OPTIONS?

Your participation is voluntary so you have the right to decline to participate or to withdraw from this research study at any time without any penalty or loss of benefits to which you would be entitled outside of the study. Choosing not to participate will not affect the care you receive at Cedars-Sinai Health System.

The alternative is not to participate. You will receive the same standard of clinical care whether you participate or not.

7. WILL MY INFORMATION BE KEPT CONFIDENTIAL?

We will do our best to make sure that the personal information collected as part of this study is kept private. However, we cannot guarantee total privacy. A copy of your research consent and authorization forms may be filed in your electronic medical record at CSMC. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other identifiable personal information will not be

used. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include: accrediting agencies, government and regulatory groups (such as Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), etc.), safety monitors, companies that sponsor the study, and authorized representatives of the sponsor.

The study team will facilitate any required access to your records by authorized representatives of the Sponsor to verify the information collected for the study.

You may, depending on the circumstances of the study and applicable law, be asked to sign a separate "Authorization Form" that outlines with whom your information may be shared for the purposes of this research and under what circumstances.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

8. WHAT IF I BECOME ILL OR INJURED BECAUSE OF TAKING PART IN THIS STUDY?

Contact your researcher at once if you feel that you are ill or have been injured because of taking part in this study. If it is a medical emergency, call 911 or go to an emergency room. Promptly notify your researcher of your situation at the phone number listed on page 1 of this consent form.

Who pays for my research related illness or injury?
Cedars-Sinai has no plans to pay for costs associated with the treatment of research-related injury or illness. We will make every effort to seek reimbursement from your health plan. However, you will be responsible for any deductibles and co-payments required under your health plan and for any claims ultimately denied by your health plan. Financial assistance may be available under Cedars-Sinai's Charity Care Policy and Procedure. If you feel that you have had a research-related injury and need financial assistance, please contact the IRB Office at 310-423-3783.

9. FINANCIAL CONSIDERATIONS

Costs of Participation

Please review the attached Appendix A flowchart for a listing of items, drugs and services that will be billed to you and/or your insurance and those that will be covered by the study sponsor.

Only items, drugs and services that are reasonable and necessary for your medical care throughout the study will be billed to your insurance. You remain responsible for all deductibles, co-pays, and balances under your health benefit plan. If your insurance company does not pay, you will be billed for those charges. You should check with your health benefit plan if you have questions or concerns about your insurance coverage.

Compensation for Participating
You will be reimbursed $300.00 at the completion of the PET/CT scans visit for your time and travel involved in coming to the study visit.

You may be required to complete a W-9 Form in order to receive payment. The W-9 Form will be maintained by our accounting department at Cedars-Sinai. Although any amount of payment may be reportable (check with a tax professional if you have questions about your obligations), if total payment by Cedars-Sinai is $600 or more in a calendar year, a 1099 Form will be filed with the IRS in accordance with federal tax law.

If you are a Cedars-Sinai employee, you should provide your employee identification number to the research team so that your payment can be appropriately processed through Payroll. For your own protection and to comply with tax laws, your payment for participation will be reported to the IRS together with other compensation you receive from Cedars-Sinai.

Financial Interest in the Research
The PI and institution have no potential financial conflict of interest with respect to this study.

10. WHAT IF I HAVE QUESTIONS OR PROBLEMS?

Please contact one of the investigators listed on the first page of this form for questions or concerns about the research.

If you have questions, problems, or concerns that you want to discuss with someone who is not associated with this study, or want to offer suggestions or feedback, please contact:

Cedars-Sinai Human Research Protection Program (HRPP) Phone: (310) 423-3783
Email: ResearchConcerns@cshs.org

The Cedars-Sinai HRPP has been established to protect the rights and welfare of research participants. You may also contact the Cedars-Sinai HRPP if you want to offer input or obtain information regarding the study.

11. CONSENT PROVISIONS

If you sign this form below, it means that:

(1) You have taken the time to carefully read and understand the information presented in this informed consent form; you should discuss it with others, and if appropriate seek a second opinion to make an informed decision;
(2) The information concerning the research study and its involved procedures has been fully explained to you and your questions have been answered to your satisfaction;
(3) You have received and understand all of the information you desire regarding your participation in the research study;
(4) You have considered the potential risks, any anticipated benefits and alternatives (and their relative risks and benefits) of participation;
(5) You are voluntarily agreeing to participate in this research study;
(6) You understand that by consenting to participate in the research, you are not giving up any of your legal rights;
(7) You understand that you have the right to be informed of significant new findings related to this research study which may affect your willingness to continue participating in this study; and

(8) You have been provided with a copy of the "Experimental Subject's Bill of Rights", if applicable to this research study, and have been provided with an opportunity to ask questions regarding the Bill of Rights.

We will give you a copy of this signed and dated consent form and a signed copy of the Experimental Subject's Bill of Rights.

SIGNATURE BY THE PARTICIPANT:

_____	_____	_____
Name of Participant (Print)	Signature of Participant	Date of Signature

SIGNATURE BY THE INVESTIGATOR:
I have personally explained the research to the participant in non-technical terms, answered all questions, and attest that he/she freely consents to participate. The participant has been provided with the Experimental Subject's Bill of Rights.

_____	_____
Signature of the Investigator Who Obtained Consent	Date of Signature

SIGNATURE BY THE INTERPRETER/WITNESS

(Signature of an interpreter is only required when a non-English speaking subject is consented with the assistance of an interpreter and an IRB-approved 'short form.' The witness may be any person who is conversant in both English and the language of the Non-English speaking subject, such as the interpreter (the certified hospital interpreter), study staff, a family member, or other person. The witness signs the consent forms to confirm that the oral interpretation occurred.)

_____	_____
Signature of Interpreter/Witness	Date of Signature

CEDARS-SINAI MEDICAL CENTER

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

In accordance with California Health and Safety Code 24172, any person who is required to consent to participate as a subject in a research study involving a medical experiment or who is requested to consent on behalf of another has the right to:

1. Be informed of the nature and purpose of the experiment.

2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized.

3. Be given a description of any attendant discomforts and risks to the subject reasonably to be expected from the experiment.

4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.

5. Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and their relative risks and benefits.

6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.

7. Be given an opportunity to ask any questions concerning the experiment or the procedure involved.

8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.

9. Be given a copy of any signed and dated written consent form used in relation to the experiment.

10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

_____ _____

Signature of Experimental Subject **Date**

Distribution instruction for researchers:

The signed (i) Consent form, (ii) Authorization for Use and Disclosure of Identifiable Health Information and (iii) "Experimental Subject's Bill of Rights" (the latter required if the research study involves medical interventions)* should be distributed to:

1) Medical Chart
2) Research Participant
3) Pharmacy (if a drug study)
4) Principal Investigator's research records (original)

APPENDIX A: FLOWCHART OF PROCEDURES

Procedures	Baseline	Visit 2 (Pre-Operative PET Scan)	Follow-up Phone Call	Visit 3 (Surgical Day)
	(-28 days)	(-7 to 0 days)	(-4 - +3 Days)	Day 0
Standard of Care Procedures: Items, drugs and services that are part of regular care and would be done even if you did not take part in this research study. These will be billed to you and/or your insurance company.				
Medical History Review	X			
Medication Review	X	X	X	
Vital Signs x 3		X		
Physical Exam		X		
Electrocardiogram x 3		X	-	
Pre-op blood tests including Fasting lipid panels, C-reactive protein and HgBA1C1	X[1]	X[1]	-	
Pregnancy test, ***if applicable***		X		
IV (intravenous) line inserted		X		
Carotid Endarterectomy or Stenting of Carotid Artery				X
MRI/MRA Imaging[2]		X		
Research Related Procedures: Items and services done for research purposes only. These will NOT be billed to your insurance company.				
Subject Informed Consent	X			
Inclusion/Exclusion Criteria	X			
PET/MR[2] Imaging with 18-flotegatilde		X		
Adverse Events	As they occur			
Sample of carotid artery plaque removed				X

[1]If labs been collected within 30 days prior to the research imaging tests, no blood will be drawn to check your kidney function.
[2] Within 96 hours of stroke or TIA (if applicable; "Symptomatic" subjects only)
[3] Baseline & Screening visits may be combined and performed in a single visit.

APPENDIX B: Detailed Description of Common Medical Procedures Performed for Research Purposes and Associated Risks

The procedures listed below are often performed as part of routine care for a person with your condition. They are being repeated, or performed more frequently as part of this research. However, the risks associated with each procedure should be comparable to what you would experience even if you were undergoing the procedure outside this research study.

Study Procedure	Related Risks
Blood draw: A needle is placed in the vein in your arm to draw blood	Blood drawing may cause some pain and has a small risk of bleeding, bruising, or infection at the puncture site. There is also a small risk of fainting.
Histology and Immunohistochemistry: During your carotid endarterectomy(CEA), atherosclerotic plaque will be removed. A sample of this plaque will be collected and taken to the histology core facility at Lerner Research Institute at the Cleveland Clinic, Cleveland, OH.	There's no pain or risk associated with the removal of the plaque from your carotid artery during the CEA.
Urine Pregnancy test: This will only need to be done if you are a woman of childbearing potential. This will need to be checked prior to scheduling your research imaging tests. If your tests are schedules more than 2 days (48 hours) since first checked, this test will need to be rechecked on the day of your research imaging testing.	There's no pain or risk associated with a urine pregnancy test.
Electrocardiogram (ECG): abbreviated as EKG or ECG – is a test that measures the electrical activity of the heartbeat using electrodes (disposable adhesive discs placed on the skin).	There's no pain or risk associated with having an electrocardiogram. When the disposable adhesive discs are removed from your skin, there may be some minor skin discomfort or irritation. You may experience temporary discomfort (pulling on the skin/skin hair) during removal of the patches. This hair may be shaved for patch placement.
Intravenous (IV) lines: You will receive the study drug or other medications or contrast agent through an intravenous (IV) line. An IV line is a small tube that is attached to a catheter and inserted by needle into a vein usually in your hand or arm. Qualified medical professionals will place IV lines for use in this study.	IV lines are usually safe and well tolerated and complications are rare, but can include phlebitis (swelling of the vein) and infection. The IV may come out accidentally or blood may leak around the line. If the IV is not in the vein, medication or fluid can enter the surrounding soft tissues, and can be associated with swelling, discomfort, bruising and irritation. Rarely, a clot can develop in the IV line itself. If this happens, the staff may remove the old IV line and start a new IV line. There is also a small risk of feeling lightheaded and fainting.
Physical Exam: Includes height, weight, vital signs (heart rate and blood pressure)	There are no physical risks associated with these procedures.
Concomitant Medications: You will be asked about your previous and current medications that you take.	There are no physical risks associated with these procedures.

Medical History Review: You will be asked about your medical and surgical history	There are no physical risks associated with this procedure.
Demographic Information: You will be asked about your age, gender, race, ethnicity	There are no physical risks associated with these procedures.