Initial Review Submission Packet (Version 1.0)

1.0 Initial Review Submission Packet

1.1 Today's Date:

03/21/2014

1.2 Study Title:

Neuronal regulation of salivary stem cells

1.3 IRB #:

1.4 Principal Investigator:

[redacted]

1.5 * Lay summary (1 to 3 brief sentences):

Salivary glands are irreversibly damaged after treatment with radiotherapy for head and neck cancer, and this substantially reduces oral health and quality of life. Stem cell therapy is a promising strategy to regenerate damaged tissue but the identity of stem cells and the mechanisms that regulate their behavior are not known. This project aims to identify salivary gland stem/progenitor cells that contribute to repair and regeneration after damage as well as the signals that control these events in order to develop targeted regenerative approaches to reverse salivary dysfunction.

1.6 * This submission is a:

(•) New study (never been approved before)

1.7 New Question Text Dec, '13 If this is a resubmission of a withdrawn study, please provide the original Study Number:

1.8 Special processing instructions or information about the submission:

URGENT: NIH JIT due April 1st 2014

The investigator requests fast processing for a JIT request by NIH.

2.0 CHR Application Form

2.1 * Attach the IRB application you completed for this protocol:

Edit/ View	Version	Title
	1.1	Study Application (Version 1.1) - Attached

3.0 Other Study Documents

3.1 Attach the other study documents (e.g. protocol, investigators brochure, recruitment materials, instruments, case report forms, study handouts or other miscellaneous documents):

Version	Sponsor Version	Title	Category	Expiration Date	Document Outcome	View Document
1.0		preliminary data for human fetal studies	Other		Approved	447.55 KB
1.0		P0062778 research Plan	Grant (pertinent portion of)		Approved	7.61 MB

Study Application (Version 1.0)

1.0 General Information

***Enter the full title of your study:**

Neuronal regulation of salivary stem cells

***Enter the study alias:**

R01
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

2.0 Add departments

2.1 and Specify Research Location:

Is Primary?	Department Name
◉	[redacted]

3.0 List the key study personnel: (Note: external and affiliated collaborators who are not in the UCSF directory can be identified later in the Qualifications of Key Study Personnel section at the end of the form)

3.1 *Please add a Principal Investigator for the study:

[redacted]

Select if applicable

Department Chair Resident

Fellow

If the Principal Investigator is a Fellow, the name of the Faculty Advisor must be supplied below.

3.2 If applicable, please select the Research Staff personnel

A) Additional Investigators

[redacted]

B) Research Support Staff

3.3 *Please add a Study Contact

[redacted]

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

3.4 If applicable, please add a Faculty Advisor/Mentor:

3.5 If applicable, please select the Designated Department Approval(s)

[redacted]

Add the name of the individual authorized to approve and sign off on this protocol from your Department (e.g. the Department Chair or Dean).

4.0 Qualifications of Key Study Personnel

4.1 November, 2015 - NEW Definition of Key Study Personnel and CITI Training Requirements:

UCSF Key Study Personnel include the Principal Investigator, other investigators and research personnel who are directly involved in conducting research with study participants or who are directly involved in using study participants' identifiable private information during the course of the research. Key Personnel also include faculty mentors/advisors who provide direct oversight to Postdoctoral Fellows, Residents and Clinical Fellows serving as PI on the IRB application. **The IRB requires that all Key Study Personnel complete Human Subjects Protection Training through CITI prior to approval of a new study, or a modification in which KSP are being added. More information on the CITI training requirement can be found on our website.**

List the study responsibilities and qualifications of any individuals who qualify as Key Study Personnel (KSP) at UCSF and affiliated sites ONLY by clicking the "Add a new row" button. This information is required and your application will be considered incomplete without it.

KSP Name	Description of Study Responsibilities	Qualifications
[redacted]		

5.0 Initial Screening Questions - Updated 9/13

(Note: You must answer every question on this page to proceed).

If you are converting to the new form, check questions 5.4, 5.6, 5.7, 5.8 and 5.10 before saving and continuing to the next section.

5.1 * Application type:

- ○ Full Committee
- ◉ Expedited
- ○ Exempt

5.2 * Risk level (Help Text updated 9/13):

- ◉ Minimal risk
- ○ Greater than minimal risk

5.3 * Subject contact:

- ○ Yes (including phone, email or web contact)
- ◉ No (limited to medical records review, biological specimen analysis, and/or data analysis)

5.4 * Funding (past or present):

- ◉ Funded or will be funded (external sponsor, gift, program or specific internal or departmental funds)
- ○ Unfunded (no specific funds earmarked for this project)
- ○ Unfunded student project

5.5 * The Principal Investigator and/or one or more of the key study personnel has financial interests related to this study:

○ Yes ◉ No

If **Yes**, the Conflict of Interest Advisory Committee (COIAC) office may contact you for additional information.

5.6 * This is an investigator-initiated study:

◉ Yes ○ No

5.7 * This study ONLY involves retrospective records review and/or identifiable biospecimen analysis:

○ Yes ◉ No

5.8 * This is a clinical trial:

○ Yes ◉ No

Clinical Trial Registration
"NCT" number for this trial:

5.9 * This is a multicenter study:

○ Yes ◉ No

5.10 * This application involves the study of unapproved or approved drugs, devices, biologics or in vitro diagnostics:

○ Yes ◉ No

5.11 * This application involves a Humanitarian Use Device:

◉ No
○ Yes, and it includes a research component
○ Yes, and it involves clinical care ONLY

5.12 * This study involves human stem cells (including iPS cells and adult stem cells), gametes or embryos:

◉ No
○ Yes, and requires CHR and GESCR review
○ Yes, and requires GESCR review, but NOT CHR review

5.13 * This is a CIRB study (e.g. the NCI CIRB will be the IRB of record):

○ Yes ◉ No

5.14 * This application includes a request to rely on another IRB (other than NCI CIRB):

○ Yes ◉ No

Note: If this request is approved, the CHR will **NOT** review and approve this study. Another institution will be the IRB of record.

6.0 Expedited Review Categories

6.1 * If you think this study qualifies for expedited review, select the regulatory category(ies) that the research falls under:

Category 1: A very limited number of studies of approved drugs and devices

Category 2: Blood sampling

Category 3: Noninvasive specimen collection (e.g. buccal swabs, urine, hair and nail clippings, etc.)

Category 4: Noninvasive clinical procedures (e.g. physical sensors such as pulse oximeters, MRI, EKG, EEG, ultrasound, moderate exercise testing, etc.)

Category 5: Research involving materials (data, documents, records, or specimens) that were previously collected for either nonresearch or research purposes

Category 6: Use of recordings (voice, video, digital or image)

Category 7: Low risk behavioral research or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies

7.0 Funding

7.1 Identify all sponsors and provide the funding details. If funding comes from a Subcontract, please list only the Prime Sponsor: **Note: we require only a P Number *OR* an A Number for**

funding coming through UCSF. Please avoid these common errors in funding documentation:

- **DO NOT add the A Number if a P Number was already provided OR update the A Number field when a new funding cycle begins. The IRB does NOT use this information or want these changes made.**
- **DO NOT add a grant continuation as a new funding source.**

External Sponsor:

View Details	Sponsor Name	Sponsor Type	Awardee Institution:	Contract Type:	Project Number	UCSF RAS System Award Number ("A" + 6 digits)
⊟	NIH Natl Inst Dental & Craniofacial Res.	01	UCSF	Grant	P0062778	

Sponsor Name:	NIH Natl Inst Dental & Craniofacial Res.
Sponsor Type:	01
Sponsor Role:	Funding
CFDA Number:	
Grant/Contract Number:	1R01DE024188-01
Awardee Institution::	UCSF
Is Institution the Primary Grant Holder:	Yes
Contract Type:	Grant
Project Number:	P0062778
UCSF RAS System Award Number ("A" + 6 digits):	
Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	
PI Name: (If PI is not the same as identified on the study.)	
Explain Any Significant Discrepancy:	

Gift, Program, or Internal Funding (check all that apply):

Funded by gift (specify source below)
Funded by UCSF or UC-wide program (specify source below)
Specific departmental funding (specify source below, if applicable)

List the gift, program, or departmental funding source:

7.2 If you tried to add a sponsor in the question above and it was not in the list, follow these steps:

- **If funding has already been awarded or the contract is being processed by the Office of Sponsored Research (OSR) or Industry Contracts Division (ICD), your sponsor is already in the**

system and the project has an eProposal Proposal or Award number. Check with your department's OSR Staff or ICD Officer to ask how the sponsor is listed in the UC sponsor list and what the Proposal or Award number is. Click here to find your OSR staff and here to find your ICD staff.

- **If your sponsor is not yet in the list, enter it in the box below.**

○ Sponsor not in list

Only if your sponsor is not yet in the list, type the sponsor's name:

If the funding is administered by the UCSF Office of Sponsored Research, your study will not receive CHR approval until the sponsor and funding details have been added to your application.

7.3 * This study is currently supported in whole or in part by Federal funding OR has received ANY Federal funding in the past (Help Text updated 9/13):

◉ Yes ○ No

If **yes**, indicate which portion of your grant you will be attaching:

The Research Plan, including the Human Subjects Section of your NIH grant or subcontract

For other federal proposals (contracts or grants), the section of the proposal describing human subjects work

The section of your progress report if it provides the most current information about your human subjects work

The grant is not attached. The study is funded by an award that does not describe specific plans for human subjects, such as career development awards (K awards), cooperative agreements, program projects, and training grants (T32 awards) OR UCSF (or the affiliate institution) is not the prime recipient of the award

8.0 Sites

8.1 Institutions (check all that apply):

8.2 Check all the other types of sites not affiliated with UCSF with which you are cooperating or collaborating on this project (Help Text updated 9/13):

Other UC Campus

Other institution

Other community-based site

Foreign Country

List the foreign country/ies:

8.3 Check any research programs this study is associated with:

Cancer Center
Center for AIDS Prevention Sciences (CAPS)
Global Health Sciences
Immune Tolerance Network (ITN)
Neurosciences Clinical Research Unit (NCRU)
Osher Center
Positive Health Program

9.0 Study Design

9.1 * Study design (Help Text updated 9/13):

Human fetal tissue is collected by [redacted] 6-24 weeks gestation each week for ongoing studies.

Human adult salivary tissue was previously colelcted by [redacted] from male and female patients of any age.

9.2 If this is a clinical trial, check the applicable phase(s) (Help Text updated 9/13):

Phase I
Phase II
Phase III
Phase IV

10.0 Scientific Considerations

10.1 Hypothesis (Help Text updated 9/13):

This study has a hypothesis:

(•) Yes ( ) No

If yes, state the hypothesis or hypotheses:

We postulate that discrete epithelial progenitor cells in the adult mouse and human salivary gland regenerate acini during homeostasis and injury in response to neuronal signals.

10.2 * List the specific aims:

Specific Aim1: Define the mechanisms by which parasympathetic nerves regulate acinar cell fate
Specific Aim 2: Determine the contribution of salivary progenitor cells and neuronal signaling to adult homeostasis and repair

Specific Aim 3: Identify human epithelial progenitor cells in fetal and adult salivary gland

10.3 Statistical analysis:

This protocol examines human tissue in Aim3, which is the identification of progenitor cells. Progenitor cells will be identified and counted using human fetal cell culture and immunohistochemistry. We will also perform qPCR to identify genes upregulated in these cells. We calculate the mean, standard deviation and standard mean of data generated and using the Student's **t**-test to compare two different groups and one-way analysis of variance to compare more than two experimental groups. For qPCR analysis, a false discovery rate (*Q*) for multiple unpaired t-tests is set to 5%.

10.4 If this study has undergone scientific or scholarly review, please indicate which entity performed the review:

Cancer Center Protocol Review Committee (PRC) (Full approval is required prior to final CHR approval for cancer-related protocols.)

CTSI Clinical Research Center (CRC) advisory committee

Departmental scientific review

Other:

Specify **Other**:

NIH

11.0 Background

11.1 Background:

Salivary gland (SG) dysfunction severely compromises the oral health and quality of life of patients: saliva protects the oral mucosa, fascilitates food digestion and articulation, and aids in the remineralization of dental hard tissues (**1**). Dry mouth or xerostomia can occur from irreversible pathological injury due to the autoimmune disease Sjogren's Syndrome (1-2 million in USA) and also from therapeutic radiation for head and neck cancer where SGs are inadvertently irradiated along with the tumor (~50,000 cases/year). Unfortunately, there are no available treatments for salivary dysfunction. A potential regenerative approach for restoring salivary function is stem cell therapy where autologous stem/progenitor cells are transplanted into the injured organ (**2**) or surviving stem cells within the tissue are reactivated (**3**). A number of putative progenitor cell populations have been identified in the mouse SG (**2**, **4-6**) and to a much lesser extent in the human SG (**7**). Despite these important observations, **the identity of salivary stem/progenitor cells that contribute to tissue homeostasis, regeneration and /or repair and the regulatory mechanisms controlling their cell fate are poorly understood.**

In this proposal we seek to understand the contribution of discrete epithelial progenitor cell populations to epithelial lineages in mouse and human SGs and determine how signals from parasympathetic nerves (ACh and Nrg1-III) promote an acinar cell fate (**Fig.1**). Parasympathetic innervation is required for the maintenance of progenitor cells and the development and regeneration of acini in salivary glands (**5**), yet the mechanisms by which nerves achieve these outcomes and the identity of the progenitor cells involved are unclear. Our recent finding that parasympathetic innervation is severely reduced in irradiated human SGs, but that putative progenitor cells (marked by keratin (K)-5+ and Sox2+) survive (**8**) (**Fig.2**) highlights the critical importance of defining neuronal-progenitor cell communication for the development of regenerative stratgies to reverse salivary dysfunction. We therefore postulate that discrete epithelial progenitor cells in the adult mouse and human SG regenerate acini during homeostasis and injury in response to neuronal signals. **Testing this hypothesis will identify human salivary progenitor cells and neuronal signaling mechanisms that regulate progenitor**

cell fate. Our findings will significantly impact the feasibility of targeted stem cell therapy for long-term functional restoration of SGs. In addition, the outcome will likely translate to regeneration of other organ systems innervated by the parasympathetic nervous system.

This study is innovative in its characterization of novel progenitor cells in the **human SG**. There have been no studies of human fetal salivary progenitors, and few of human adult salivary progenitor cells. The use of fetal tissue has significant advantages in understanding human progenitor cells in that it allows for the evaluation of human developmental populations, the isolation of progenitor populations and, as fetal cells have a competitive advantage over adult cells, successful ex vivo culture and in vivo engraftment are highly feasible (**9**). Importantly, our strategy of isolating human progenitors is not dependent on extrapolation from mouse models but is based on transcriptional analysis and ex vivo self-renewal/differentiation capability in human tissue. This novel and powerful approach will reveal new insights into progenitor cell identity and mechanisms regulating their behavior.

11.2 Preliminary studies:

Human salivary glands do not regenerate after damage induced by therpauetic radiation for head and neck cancer. We postulate that this may be due to a loss in neuronal function that maintains and stimulate progenitor cells to repair tissue. In support of this, we have found reduced nerve supply to putative progenitor cells in the human tissue after radiation ([redacted]; see ref 8). We have also found that progenitor cell populations are differentially affected by radiation damage (ref.8).
in regards to identification of true progenitor cells in the fetal tissue, we have initial data supporting our ability to isolate progenitor cells for clonal expansion in vitro i.e. we show that these cells are capable of proliferating in response to stimuli. We have performed gene expression analysis on these cells contain factors known to be involved in sel-renewal (e.g. Sox2). Further studies are necessary to truly identify the progenitor cells and whether these are capable of differentiating into multiple cell types. We have attached a figure containing data for this section.

11.3 References:

1. Grundmann O, Mitchell GC, Limesand KH. Sensitivity of salivary glands to radiation: from animal models to therapies. J Dent Res. 2009;88(10):894-903. Epub 2009/09/29. doi: 10.1177/0022034509343143. PubMed PMID: 19783796; PubMed Central PMCID: PMC2882712.
2. Lombaert IM, Brunsting JF, Wierenga PK, Faber H, Stokman MA, Kok T, et al. Rescue of salivary gland function after stem cell transplantation in irradiated glands. PLoS One. 2008;3(4):e2063. Epub 2008/05/01. doi: 10.1371/journal.pone.0002063. PubMed PMID: 18446241; PubMed Central PMCID: PMC2329592.
3. Banh A, Xiao N, Cao H, Chen CH, Kuo P, Krakow T, et al. A novel aldehyde dehydrogenase-3 activator leads to adult salivary stem cell enrichment in vivo. Clin Cancer Res. 2011;17(23):7265-72. Epub 2011/10/15. doi: 10.1158/1078-0432.ccr-11-0179. PubMed PMID: 21998334; PubMed Central PMCID: PMC3544360.
4. Rugel-Stahl A, Elliott ME, Ovitt CE. Ascl3 marks adult progenitor cells of the mouse salivary gland. Stem cell research. 2012;8(3):379-87. Epub 2012/03/01. doi: 10.1016/j.scr.2012.01.002. PubMed PMID: 22370009; PubMed Central PMCID: PMC3319487.
5. Knox SM, Lombaert IM, Reed X, Vitale-Cross L, Gutkind JS, Hoffman MP. Parasympathetic innervation maintains epithelial progenitor cells during salivary organogenesis. Science. 2010;329(5999):1645-7. Epub 2010/10/12. doi: 10.1126/science.1192046. PubMed PMID: 20929848.
6. Arnold K, Sarkar A, Yram MA, Polo JM, Bronson R, Sengupta S, et al. Sox2(+) adult stem and progenitor cells are important for tissue regeneration and survival of mice. Cell stem cell. 2011;9(4):317-29. Epub 2011/10/11. doi: 10.1016/j.stem.2011.09.001. PubMed PMID: 21982232; PubMed Central PMCID: PMC3538360.
7. Feng J, van der Zwaag M, Stokman MA, van Os R, Coppes RP. Isolation and characterization of human salivary gland cells for stem cell transplantation to reduce radiation-induced hyposalivation. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2009;92(3):466-71. Epub 2009/07/25. doi: 10.1016/j.radonc.2009.06.023. PubMed PMID: 19625095.
8. [redacted]

9. Taylor PA, McElmurry RT, Lees CJ, Harrison DE, Blazar BR. Allogenic fetal liver cells have a distinct competitive engraftment advantage over adult bone marrow cells when infused into fetal as compared with adult severe combined immunodeficient recipients. Blood. 2002;99(5): 1870-2. Epub 2002/02/28. PubMed PMID: 11861310.

If you have a separate bibliography, attach it to the submission with your other study documents.

12.0 Sample Size and Eligibility

12.1 Number of subjects that will be enrolled at UCSF and affiliated institutions:

12.2 Total number of subjects that will be enrolled at all sites (Help Text updated 9/13):

12.3 Estimated number of people that you will need to consent and screen here (but not necessarily enroll) to get the needed subjects:

12.4 Explain how and why the number of subjects was chosen (Help Text updated 9/13):

12.5 * Eligible age range(s):

0-6 years
7-12 years
13-17 years
18+ years

12.6 Inclusion criteria:

12.7 Exclusion criteria:

12.8 There are inclusion or exclusion criteria based on gender, race or ethnicity:

○ Yes ○ No

If **yes**, please explain the nature and rationale for the restrictions:

13.0 Other Approvals and Registrations

13.1 * Do any study activities take place on patient care units:

○ Yes ◉ No

If **Yes**, attach a letter of support for the study from the involved patient care manager(s).

13.2 * **Does your protocol involve any radiation exposure to patients/subjects? The UCSF Radiation Safety Committee requires review of your protocol if it includes administration of radiation as part of standard of care OR research exposures:**

○ Yes ◉ No

13.3 * **This study may generate genetic data that may be broadly shared (e.g. submitted to NIH for Genome-Wide Association Studies (GWAS) in dbGaP, TCGA, etc):**

○ Yes ◉ No

13.4 * **This study involves administration of vaccines produced using recombinant DNA technologies to human subjects:**

○ Yes ◉ No

13.5 * **This study involves human gene transfer (NOTE: Requires NIH Recombinant DNA Advisory Committee (RAC) review prior to CHR approval):**

○ Yes ◉ No

13.6 This study involves other regulated materials and requires approval and/or authorization from the following regulatory committees:

Institutional Biological Safety Committee (IBC)

Specify BUA #:

BU089354-01A

Institutional Animal Care and Use Committee (IACUC)

Specify IACUC #:

Radiation Safety Committee

Specify RUA #:

Radioactive Drug Research Committee (RDRC)

Specify RDRC #:

Controlled Substances

14.0 Procedures: No Subject Contact

14.1 Check all that apply:

Retrospective Chart Review
Biological Specimen Analysis
Specimen Banking for Future Research
Data Analysis

UCSF is serving as the Coordinating Center only

14.2 Source:

Salivary tissue adult biopsies are from [redacted] and [redacted]

14.3 The source obtained consent from subjects to use the biological specimens or data for the research proposed in this study:

(•) Yes ( ) No

If **no**, explain:

14.4 The source has IRB Approval to obtain and possess the biological specimens or data:

(•) Yes ( ) No

If **no,** explain:

14.5 Type of records, biological specimens, and data:

biopsy samples

14.6 Dates for the records, biological specimens, or data that will be used:

From:

06/01/2012

To:

01/01/2014

OR

Indefinite (for repositories and other ongoing research resources)

14.7 Variables that will be abstracted from the records or received with the biological specimens or data set:

age, sex, previous radiation exposure and chemotherapy

15.0 Confidentiality and Privacy

15.1 Plans for maintaining privacy in the research setting:

The PI has no access to and will ask for no identifers of human adult patient samples or fetal samples

15.2 Possible consequences to subjects resulting from a loss of privacy:

15.3 Study data are:

Derived from the Integrated Data Repository (IDR) or The Health Record Data Service (THREDS) at SFGH
Derived from a medical record (e.g. APeX, OnCore, etc. Identify source below)
Added to the hospital or clinical medical record
Created or collected as part of health care
Used to make health care decisions
Obtained from the subject, including interviews, questionnaires
Obtained from a foreign country or countries only
Obtained from records open to the public
Obtained from existing research records
None of the above

If **derived from a medical record**, identify source:

15.4 Identifiers may be included in research records:

○ Yes ◉ No

If **yes**, check all the identifiers that may be included:

Names
Dates
Postal addresses
Phone numbers
Fax numbers
Email addresses
Social Security Numbers*
Medical record numbers
Health plan numbers
Account numbers
License or certificate numbers
Vehicle ID numbers
Device identifiers or serial numbers
Web URLs
IP address numbers
Biometric identifiers
Facial photos or other identifiable images
Any other unique identifier

* Required for studies conducted at the VAMC

15.5 Identifiable information might be disclosed as part of study activities:

○ Yes ◉ No

If **yes**, indicate to whom identifiable information may be disclosed:

The subject's medical record
The study sponsor
Collaborators
The US Food & Drug Administration (FDA)
Others (specify below)
A Foreign Country or Countries (specify below)

If **Others**, specify:

15.6 Indicate how data are kept secure and protected from improper use and disclosure (check all that apply): NOTE: Whenever possible, do not store subject identifiers on laptops, PDAs, or other portable devices. If you collect subject identifiers on portable devices, you MUST encrypt the devices.

Data are stored securely in My Research
Data are coded; data key is destroyed at end of study
Data are coded; data key is kept separately and securely
Data are kept in a locked file cabinet
Data are kept in a locked office or suite
Electronic data are protected with a password
Data are stored on a secure network
Data are collected/stored using REDCap or REDCap Survey
Data are securely stored in OnCore

15.7 Additional measures to assure confidentiality and protect identifiers from improper use and disclosure, if any:

15.8 This study may collect information that State or Federal law requires to be reported to other officials or ethically requires action:

○ Yes ◉ No

Explain:

15.9 This study will be issued a Certificate of Confidentiality:

○ Yes ◉ No

16.0 Subjects

16.1 Check all types of subjects that may be enrolled:

Inpatients
Outpatients
Healthy volunteers
Staff of UCSF or affiliated institutions

16.2 Additional vulnerable populations:

Children
Subjects unable to consent for themselves
Subjects unable to consent for themselves (emergency setting)
Subjects with diminished capacity to consent
Subjects unable to read, speak or understand English
Pregnant women
Fetuses
Neonates

Prisoners

Economically or educationally disadvantaged persons

Investigators' staff

Students

Explain why it is appropriate to include the types of subjects checked above in this particular study:

Describe the additional safeguards that have been included in the study to protect the rights and welfare of these subjects and minimize coercion or undue influence:

17.0 Waiver of Consent/Authorization

(August, 2013)

17.1 * I affirm that subjects' rights and welfare will not be adversely affected by waiving informed consent:

(•) Yes

17.2 * It is not practicable to obtain informed consent because (check all that apply):

Many subjects are no longer being followed at the institution or are deceased

The attempt to contact subjects poses a greater risk than this study

The large number of records required makes it impracticable to contact all potential subjects

The researchers do not know the identity of the study subjects and therefore cannot contact them

The data being used was collected under a different CHR-approved study and subjects gave their consent for data to be used in research of this type

Other (explain below)

If **Other**, explain:

17.3 * Subjects will be provided with pertinent information after their participation:

( ) Yes (•) No

* Please explain why or why not:

We have no identifiers of subjects i.e. samples are anonymized and the PI has no access to records.

18.0 End of Study Application

18.1 End of Study Application Form **To continue working on the Study Application: Click on the section you need to edit in the left-hand menu. Remember to save through the entire Study Application after making changes. If you are done working on the Study Application: Click Save and Continue. If this is a new study, you will automatically enter the Initial Review Submission Packet form, where you can attach consent forms or other study documents. Review the Initial Review Submission Checklist for a list of required attachments. Answer all questions and attach all required documents to speed up your approval.**

Continuing Review Submission Form (Version 1.0)

1.0

Continuing Review Form

To copy last year's form, please review the Quick Guide titled "Submitting Post-Approval Forms" in the system "Help" area for step-by-step instructions and screen shots. If prompted, make sure you 'Convert to the New Form Version' whenever you copy an old submission form.

1.1 Principal Investigator:

[redacted]

1.2 Study Title:

Neuronal regulation of salivary stem cells

1.3 Study Number:

14-13442

1.4 Expiration Date:

03/31/2015

*If the study has expired, an explanation is required at the end of the form.

1.5 Lay Summary:

Salivary glands are irreversibly damaged after treatment with radiotherapy for head and neck cancer, and this substantially reduces oral health and quality of life. Stem cell therapy is a promising strategy to regenerate damaged tissue but the identity of stem cells and the mechanisms that regulate their behavior are not known. This project aims to identify salivary gland stem/progenitor cells that contribute to repair and regeneration after damage as well as the signals that control these events in order to develop targeted regenerative approaches to reverse salivary dysfunction.

1.6 * This is a:

- (•) Continuing Review Only—no changes from last approval
- ( ) Continuing Review and Minor Modification
- ( ) Continuing Review and Major Modification

1.7 * This application includes personnel changes:

( ) Yes (•) No

1.8 * Has your study expired:

( ) Yes (•) No

If **Yes**, work on this study must stop **IMMEDIATELY**.

1.9 Outstanding Stipulations:

No Stipulation is outstanding.

2.0 Study Status

2.1 * Have any new risks been identified since the last continuing review (or since approval if this is the first continuing review):

○ Yes ◉ No

2.2 Current study status: (*choose one only*)

Study is open to accrual:

- ◉ No participants have been enrolled and no additional risks have been identified.
- ○ Participants are currently receiving study intervention.
- ○ Participants have been enrolled but none are currently receiving study intervention.
- ○ Ongoing medical record review/biological specimen analysis.

Study is closed to accrual:

- ○ Some participants are still receiving study intervention.
- ○ Study intervention is complete for all participants; research-related diagnostic tests or follow-up clinic visits are continuing.
- ○ Study intervention is complete or there was no intervention, and there is ongoing research-related follow-up contact with participants via questionnaires, phones calls, interviews, or mailings.
- ○ Study intervention is complete or there was no intervention and follow-up is limited to review of medical records or other records (no ongoing contact).
- ○ Study is in data analysis phase only.

2.3 Summary of results to date:

we have assessed a number of markers in the adult human sections that have failed to detect stem cells and are utilizing a larger antibody array.

2.4 Brief summary of plans for the coming year:

We will be screeing salivary samples with a large array of antibodies.

3.0 Recent Literature

3.1 Summary of recent literature:

A recent study (**Stem Cell Reports**. 2014 Dec 9;3(6):957-64) has isolated some putative stem cell populations from human salivary glands and a number of new markers have been identified. Other studies have identfied stem cells from other organs that may be able to incorporate into the salivary tissue, but whether these become salivary stem cells is not known (**Int J Mol Med**. 2014 Sep;34(3):749-55). Other studies have utilize

cancer salivary samples to identify possible markers, which will also be screened in our studies in normal and irradiated glands (**Biomed Res Int.** 2014;2014:132349.). Despite these studies, the identity of stem cells in human glands remains elusive, as does the effect of radiation on these cell types.

4.0 Significant Findings & Other Reportable Events

4.1 Did you report any 10-day reportable events, including complaints about the research, since the last continuing review (or since initial approval if this is the first continuing review):

○ Yes ◉ No

If **Yes,** provide a brief narrative summary of adverse events, protocol violations, safety information, and/or complaints over the past year so that CHR members can understand the overall trends:

4.2 Are you submitting any new or missed 10-day reportable events, including complaints, at this time (submit separately in system using the appropriate submission form):

○ Yes ◉ No

4.3 Plan for informing subjects of information that may affect willingness to continue participation:

If new risks have been identified since the last continuing review (or since initial approval if this is the first continuing review), explain how subjects were or will be informed of any new information and when the modification was approved if the notification already occurred:

Attach any additional documents (consent forms or contact letters) that will be used for this purpose at the end of the form.

4.4 * Does this study undergo formal on-site monitoring:

○ Yes ◉ No

4.5 * This study was audited by any external group or entity (i.e., sponsor, FDA) since its last renewal:

○ Yes ◉ No

Auditing entity:

4.6 If YES to either monitoring or auditing, describe any significant findings resulting from either the monitoring or auditing activities or state "None" if there were no significant findings:

4.7 Other reportable events:

If this is a biomedical **interventional study** did you have any **internal** (on-site) participant deaths determined to be *unrelated* to research participation?

○ Yes ◉ No

If **yes**, attach an **AE Summary Log** at the end of this form.

Is your study sponsor *requiring* that you forward any Study Sponsor **external** (off-site) Safety Reports *that are not otherwise reportable* under CHR guidelines:

○ Yes ◉ No

If **yes**, attach an **AE Summary Log** at the end of this form.

5.0 Updated Financial Disclosure

5.1 * Are there any changes in any financial interests related to this study or in any conflicts of interest of the PI or any other investigator:

○ Yes ◉ No

If **Yes**, the Conflict of Interest Advisory Committee (COIAC) office may contact you for additional information.

6.0 Attach Other Study Documents (AE Summary Log, revised documents, or new documents)

6.1 Upload AE Summary Log and/or any new or revised other documents here:

Attach the documents following these instructions:

Revised Documents: Follow these steps if you are revising currently approved documents or if you are submitting revised documents created by the study sponsor or lead site (e.g. revised protocols or investigator's brochures).

Click the Select or Revise Existing button. Click Upload the Revised Document and select the revised document from your computer. *If you need to download the current version of the document from iRIS first,* click Download Document for Editing and then Upload the Revised Document after you've updated the document. Save your work.

New Documents: Click on the Add Document button and upload your new document.

Reminder: If you are revising or adding new study documents, indicate that the continuing review includes modifications in question 1.6.

Approved Documents – No Changes: These documents do **not** need to be resubmitted during the continuing review.

NOTE: Please make sure that any tracked changes have been accepted for both consent forms and study documents. If tracked changes are submitted, they will show in the stamped PDF and you will have to submit a modification to get clean documents stamped.

Version	Sponsor Version	Title	Category	Expiration Date	Document Outcome	View Document
No Document(s) have been attached to this form.						

Continuing Review Submission Form (Version 2.0)

1.0

Continuing Review Form

Welcome to the new Continuing Review Form! Please make sure you 'Convert to the New Form Version' if prompted.

NOTE: This form now features dynamic show/hide functionality:

- **Questions will appear and disappear as you complete the form. The form now hides questions that are not relevant to your study.**
- **If the question numbers skip (e.g. 2.1, 2.4, 2.5, 2.8), it's because some questions are hidden. The form is functioning normally. For the best experience, please avoid using the Chrome browser.**

Other changes include:

- **Fewer sections**
- **Shorter form for minimal risk research and studies not involving subject contact**
- **Smarter form includes only relevant attachment sections**
- **More intuitive and complete Subject Enrollment section**
- **Elimination of the AE Summary Log for non-reportable AEs and deaths**

This form features dynamic show/hide functionality. For the best experience, please avoid using the Chrome browser.

1.1 Principal Investigator:	
[redacted]	
1.2 Study Title:	
Neuronal regulation of salivary stem cells	
1.3 Study Number:	
14-13442	
1.4 Lay Summary:	
Salivary glands are irreversibly damaged after treatment with radiotherapy for head and neck cancer, and this substantially reduces oral health and quality of life. Stem cell therapy is a promising strategy to regenerate damaged tissue but the identity of stem cells and the mechanisms that regulate their behavior are not known. This project aims to identify salivary gland stem/progenitor cells that contribute to repair and regeneration after damage as well as the signals that control these events in order to develop targeted regenerative approaches to reverse salivary dysfunction.	

1.5 * **NEW - Biospecimen Banks, Research Databases, and Recruitment Registries - Does this IRB approval ONLY cover activities such as biospecimen collection/banking, and/or collection of data in a research registry or recruitment database: (REQUIRED)**

○ Yes ◉ No

1.6 * **This is a: (REQUIRED)**

◉ Continuing Review Only—no changes from last approval
○ Continuing Review and Minor Modification
○ Continuing Review and Major Modification

1.7 * **Does this submission include personnel changes: (REQUIRED)**

○ Yes ◉ No

1.14 * **Are there any changes in any financial interests related to this study or in any conflicts of interest of the PI or any other investigator: (REQUIRED)**

○ Yes ◉ No

1.15 **Expiration Date: Hint: Click 'Refresh Constant Fields' to update the expiration date if this is a copied form.**

03/31/2016

* **Has your study expired: (REQUIRED)**

○ Yes ◉ No

1.16 **Outstanding Stipulations:**

No Stipulation is outstanding.

2.0 Study Status for No Subject Contact Studies

Note: Investigators are no longer asked to provide the number of records and/or specimens reviewed since the last approval.

2.1 * **Study Status: (REQUIRED)**

○ Study activities have not yet commenced
◉ Study in progress - data or specimens are still being collected and/or analyzed
○ Final data analysis and/or manuscript preparation

2.2 * **Have you had any reportable incidents, including a breach of confidentiality (e.g. lost or stolen laptop or other machines/devices with study data on them, hacked networks or study records left in a public place): (REQUIRED)**

○ Yes ◉ No