UC San Diego
HEALTH SYSTEM

November 1, 2013

SAGES Grant Committee
11300 West Olympic Boulevard
Suite 600
Los Angeles, CA 90064

Re: Immunofluorescence of Ghrelin Cells in a Mouse Model: Can We Visualize the Specific Cells for Removal During a Sleeve Gastrectomy?

Dear Committee Members:

Please accept this grant proposal for consideration in the 2014 SAGES research grant competition. We are excited about our research proposal regarding this feasibility study for imaging ghrelin cells in a mouse model. We believe that our proposal is the first step to determining if we can visualize, in vivo, the specific cells that should be removed during a sleeve gastrectomy or during other bariatric operations. Should we prove that this model is feasible, we can quickly utilize the technology in larger species with the ultimate goal of potential use in humans undergoing bariatric operations. If what we propose is possible, the implications in bariatric surgery are enormous as therapy could be individualized depending upon each patient's ghrelin locus.

If any additional material or information is desired, please do not hesitate to contact me. Thank you for your consideration.

Sincerely,

Bryan Sandler, MD FACS

Assistant Professor of Surgery
Division of Minimally Invasive Surgery
Department of Surgery
University of California San Diego

Immunofluorescence of Ghrelin Cells in a Mouse Model: Can We Visualize the Specific Cells for Removal During a Sleeve Gastrectomy?

Society of American Gastrointestinal and Endoscopic Surgeons Grant Proposal

November 2013

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Co-Investigator: Santiago Horgan, MD, FACS
Professor of Surgery
Chief, Division of Minimally Invasive Surgery
Director, Center for the Future of Surgery
Department of Surgery
University of California San Diego

Statement of Funds:

Funding for the salaries of investigators is provided through the UCSD department of surgery. The remaining funding for this project and its materials would be funded through this grant support.

Summary:
Ghrelin is a peptide hormone secreted by the stomach and was first described in 1999 [1, 2, 3], It is a multifunctional molecule which has a key role in regulating appetite and food intake [14]. The medical community is increasingly learning its importance based on outcomes in bariatric surgery. It is well studied that ghrelin production and utilization is altered after bariatric surgery, specifically sleeve gastrectomy. Changes in serum ghrelin levels have been proven after bariatric operations [15-23], which have been hypothesized to contribute to their long-term success. What is not known is the exact position of the ghrelin producing cells in vivo during the excision of the gastric fundus.

The use of immunofluorescence labeling and imaging has also seen increasing use in the operating room in the past decade[18-19]. Antibodies to cell-specific proteins have been coated with antibodies with the ability to emit fluorescent light which can be seen with the application of a filter in the camera system. Similar to imaging that has been used in pancreatic cancers or biliary ICG, our goal is to apply a fluorescent antibody to anti-ghrelin specific antibodies to visualize ghrelin producing cells in the stomach.

Animal models are a productive way to perform feasibility studies prior to introduction into the human setting. Many animal models have been produced, including a mouse model for emulating bariatric operations[20]. Using a mouse model, an injectable anti-ghrelin antibody that is labeled with a fluorescent-capable antibody will be injected into mice. An open operation will then be performed to expose the mucosal cells of the mouse stomach. A digital camera equipped with a filter for visualizing fluorescent wavelengths will be used to attempt seeing the specific ghrelin cells in vivo.

Once the feasibility has been proven, further studies may be performed to show the differences between ghrelin cells before and after bariatric surgery. If feasible, the application of this method could be implemented in a human for cell-specific targeting bariatric operations – including sleeve gastrectomy, roux-en-Y gastric bypass, as well as during possible endoscopic procedures with specific cellular targets.

Background:
Ghrelin, a 28 amino-acid acylated orexigenic peptide hormone secreted by the stomach, was first described in 1999 [1, 3]. It has been identified as a ligand of the growth hormone secretogogue receptor (GHS-R).

Ghrelin is a multifunctional molecule. It plays important roles in growth-hormone release and appetite stimulation. In addition, it plays various physiological roles, including control of gastric motility and acid secretion, exhibits cardiovascular effects, influences pancreatic activity [10, 11], & decreases lipid metabolism in mice [12, 13].

The central effect of ghrelin on food intake is thought to result from its direct actions on the arcuate nucleus of the hypothalamus. Additionally, plasma ghrelin levels increase preceding meals and during fasting, thus acting as a key regulator of appetite and food intake [14-16].

Several studies have confirmed that the source of most circulating ghrelin is a distinct group of endocrine cells located within the gastric oxyntic mucosa [2]. Microscopically, these gastric cells are characterized by round, compact, electron-dense secretory granules of X-type that do not have direct contact with gastric luminal contents, and tend to cluster towards the base of the gastric mucosal glands in mice [2-4, 15].

The prevalence of morbid obesity is increasing worldwide. Currently, bariatric surgeries are among the most effective and sustainable approaches for the treatment of obesity with different modes of action. A change in ghrelin levels in the serum has been proven after bariatric operations [17, 25-27]. Some of these procedures prevent rise in ghrelin levels with weight loss [28] and this has been hypothesized to contribute to their long-term success. The study of Cummings et al., which showed a profound suppression of ghrelin levels following Roux-en-Y gastric bypass, has brought the interaction of weight loss operations and the gut-brain axis into focus [23-24]. Yet there is no solid agreement as to the direction or magnitude of ghrelin level change, or even its impact on weight loss.

One area that hasn't been studied extensively is the impact of bariatric surgery on the specific ghrelin producing cells of the stomach. The main reason for not studying this in the past is the inability to visualize the cells without the use of microscopy or western blot analysis. Microscopic Ghrelin-immunoreactivity has been used to localize ghrelin cells in many different tissues and species, including mice and rats [1, 5-7]. *Humanized Renilla reniformis* green fluorescent protein was successfully used to mark the location of ghrelin-producing cells in mice model to study the physiologic characteristics of these cells under the microscope [16].

With the advent and increasing role of immunofluorescence in intra-operative visualization of tissues, a potentially new method for visualizing the ghrelin cells should be studied. Surgical oncologists are using immunofluorescence to improve resection margins in cancers [18]. General surgeons are using Indocyanin green (ICG) to visualize the biliary system to improve safety of laparoscopic cholecystectomy [19]. ICG or fluorescein can be seen with a Woods lamp or using SPY technology to assess bowel perfusion or anastomosis viability.

We have studied and found a supplier for anti-ghrelin antibodies which are able to be used in a mouse model (Thermo Scientific)[26]. These antibodies are expensive (200 micrograms for $295.00) and are the greatest hurdle in our feasibility study[26]. Our goal is to label the anti-ghrelin antibodies with a fluorescent marker called DyLight®, also from ThermoScientific. The antibody-marker complex will

then be injected into a mouse model and an Olympus OV100 digital camera with a filter capable of seeing the wavelength of fluorescent light at a range of 450-750nm, will be used to attempt direct visualization of the ghrelin producing cells in a mouse stomach.

Preliminary Experience with Fluorescence Guided Surgery in mouse models: Our co-Investigator, Dr. Bouvet, and his colleagues have developed fluorescence-guided surgery for GI malignancies in orthotopic mouse models of cancer (see images in Appendix below). In a recent study, Dr Bouvet's group evaluated a set of visible and near-infrared dyes conjugated to a tumor specific chimeric antibody for their ability to effect high resolution tumor imaging in orthotopic models of pancreatic cancer[(30)]. BxPC-3 human pancreatic cancer was orthotopically implanted into pancreata of nude mice. Mice received a single IV injection of a chimeric anti-CEA antibody conjugated to one of the following fluorophores: 488 nm group (Alexa Fluor 488 or DyLight 488); 550 nm group (Alexa Fluor 555 or DyLight 550); 650 nm group (Alexa Fluor 660 or DyLight 650) and the 750 nm group (Alexa Fluor 750 or DyLight 755). 24 hours later, the Olympus OV100 small animal imaging system was used for non-invasive and intravital fluorescence imaging of mice (Figure 1 below). Dyes were compared with respect to depth of imaging, resolution, tumor to background ratio, photobleaching and hemoglobin quenching. The longer wavelength dyes had increased depth of penetration and ability to detect the smallest tumor deposits and provided the highest tumor to background ratios, resistance to hemoglobin quenching, and specificity (Figure 2 below). The shorter wavelength dyes were more photostable. This study showed unique advantages of each dye for specific cancer imaging in a clinically relevant orthotopic model. A similar experimental approach could be taken to image ghrelin in this study.

Once our hypothesis is proved feasible, it is our goal to continue our research by creating a UCSD-specific bariatric mouse model for further studies, specifically to test the difference between ghrelin cells in the mouse stomach before and after sleeve gastrectomy and other bariatric surgery. Extensive research has been completed to determine the best model for bariatric surgery, and the mouse provide an excellent basis for moving forward with these protocols in the future.

Our overall goal would be to ultimately translate our research to use in humans. The capability to see in vivo ghrelin producing cells during a bariatric operation could lead to cell patient-specific cell-directed therapy to be performed both in a standard fashion, or with the possibility of creating an entirely endoscopic option.

- **Problem:** Inability to visualize gastric specific ghrelin producing cells in vivo.
- **Significance:** Ghrelin is known to be affected by bariatric surgery. If ghrelin cells could be specifically targeted in future operations with good efficacy, high morbidity and mortality operations could be avoided with cell-specific therapy.
- **Prior Studies:** No prior studies have been performed to attempt visualization of ghrelin producing cells with fluorescent labeled anti-ghrelin antibody.
- **Preliminary Work:** The UCSD Department of Surgical Oncology has agreed to allow use of their photo-fluorescence camera imaging techniques to determine the feasibility of the injections of anti-ghrelin antibody. Our study will be performed on mice, through an IACUC-approved protocol that has been submitted. Additionally, we have identified a supplier for the anti-ghrelin antibody which is $295 for 200 micrograms of antibody; concentrations of effective use will need to be developed. Finally, the UCSD Department of Surgical Oncology has full access to fluorescent antibody labeling techniques as well as the digital camera with applied filter for visualizing these antibodies.

Hypothesis:

Ghrelin producing cells in a mouse model are able to be visualized in vivo using fluorescent labeled anti-ghrelin antibody and specialized imaging equipment.

Methods:

Power analysis is not needed for this study as we are proving the feasibility of a specific technique, rather than proving the difference between study groups.

Mouse Model:

A total of 50 mice at the age of 8 weeks, weighing 16-20 grams will be used for this study.

Preparation of Antibody:

The preparation of antibody is provided below and given as direct instructions from Thermo Scientific for use of DyLight® Amine-Reactive Dyes

A. Protein Preparation
The optimal labeling buffer is 0.05M sodium borate buffer at pH 8.5 (Product No. 28384). When labeling with DyLight 594 NHS-Ester, prepare the protein in phosphate-buffered saline to avoid precipitation. Buffers that contain primary amines (e.g., Tris or glycine) will interfere because they react with the NHS-ester moiety. Dissolve protein directly in the labeling buffer. For each labeling reaction, use 100-500µL of purified protein sample at 1-2.5mg/mL. If the protein is already in a buffer, perform a buffer exchange into the labeling buffer by dialysis or gel filtration.
Note: The following buffers may be substituted for borate buffer: 0.1M sodium phosphate, 0.15M NaCl at pH 7.2-7.5 (e.g., Thermo Scientific BupH Phosphate Buffered Saline Packs, Product No. 28372) or 0.1M sodium carbonate at pH 8.3-9.0.

B. Labeling Reaction
Note: The DyLight NHS-Ester reagents are moisture-sensitive. Store the reagent in the original container at -20°C with desiccant.
1. Transfer the protein solution to the vial containing the dye. Mix well by vortexing up-and-down several times and incubate at room temperature for 1 hour.
2. Remove excess dye reagent from the sample using the Thermo Scientific Dye Removal Columns (Product No. 22858) or a dialysis membrane with a molecular-weight cutoff ≥ 10K.

1. Isolate 200 micrograms in PBS of anti-ghrelin antibody (one vial)
2. Conjugate with fluorescent antibody as listed above
3. Dilute to a value of 20 micrograms per ml as initial dose for anti-ghrelin antibody.
4. Injection of 4ml of labeled antibody is performed into the tail of the mouse as the imaging equipment is running to determine if cells can be visualized in real-time.
5. Need to verify anti-ghrelin antibody dose through in vivo imaging techniques below.

Equipment for In Vivo Imaging:

The Olympus OV100 allows for observation of fluorescence markers in live animals from the subcellular level to the entire animal. It also allows for time-lapse observation of a variety of physiological and pathological events. This imaging system contains the following features:
1. Four individually optimized objectives (three macrolens and one zoom lens) that are parcentered and parfocal providing a total 105-fold magnification.

2. High-sensitivity Hamamatsu Electro Multiplying (EM) CCD camera.
3. High numerical aperture (NA) optical system with rapid scanning mode that shortens exposure times and minimizes specimen damage.
4. Multiple observation channels that afford multi-channel co-imaging: bright field, GFP, RFP, 680, 750.
5. Software: scope control/image acquisition of still images and movies/image processing and analysis.

In-Vivo Imaging Technique:

1. Place the animal in the anesthesia induction chamber, turn on the Isoflurane Vaporizer Dial, and adjust the level gauge to 3%. Wait until the mouse reaches the desired depth of anesthesia by the toe-pinch test. Transfer the anesthetized mouse from the induction chamber to the OV100 imager, and immediately place the animal's muzzle into the nose cone connected to the imaging platform. Turn the isoflurane dial back to 1%. When the mouse's respiration becomes smooth and stable, imaging session can be initiated.
2. The mouse is placed on the imaging platform with abdomen side up. A 1 cm upper midline laparotomy incision extending from the xiphoid process to the lower abdominal is performed.
3. Stomach will be identified and externalized.
4. The gastrosplenic ligament connecting the left superior stomach to the spleen will be carefully divided using electrocautery thereby freeing the gastric fundus from the surrounding tissue for a full mobilization of the stomach.
5. A longitudinal stomach incision will be made, on the anterior surface of the stomach.
6. Open the OV-100 image acquisition software and set up imaging capture parameters according to manufacturer's instructions. The observation is started with 0.14×, the lowest magnification level in the GFP-LP channel. Adjust the shift control on the control module to place the stomach in the center of the view window on the computer screen. Note, from this moment on, adjustments of imaging parameters, changing the position of the imaging platform, selection of the filter sets, changing the focus, and image acquisition will all be made through the image acquisition software. Adjust the position of the platform up or down, so that the stomach will be in focus.
7. To visualize at a higher resolution, increase the magnification level to 0.56×. Since the four subzoom lenses of OV-100 are parfocal, the images will largely remain focused when the magnification levels are altered at three subzoom levels (from 0.14× to 0.89×). Therefore, only very minor adjustment is required to refocus the desired imaging field. Thereafter, the light intensity and exposure time need to be adjusted so that the intensity of the histogram remains between 90% and 100% to avoid over-exposure or under-exposure.
8. After observations with the macrolens at subzoom magnifications, random fields of vessels or areas of interest can be chosen for observation with the zoom lens for finer details and for obtaining high-resolution planner images. At the zoom level, digital magnification ranges from 1.6× to 16×.
9. Labeled anti-ghrelin antibody will then be injected through the tail of the mouse in 20 microgram increments until the fluorescence is able to be visualized in real-time.
10. Ghrelin cells will then be visualized in real-time and characterized using VisEn's near infrared (NIR) with dual channel OV-100 imaging (480 nm GFP and 680 nm near infrared)
11. Under general anesthesia, the mice will be sacrificed by cardiac puncture and exsanguinations immediately after the procedure.

12. Images will be captured in real-time and populated at each concentration level introduced to assess the feasibility.

Potential Pitfalls and Plan:

Immunofluorescence imaging in the past has consisted of labeling proteins incorporated in the cell wall. We may be unable to selectively label the ghrelin producing cells, as it is a free-floating plasma peptide, but through fluorescence wavelength variation, we hope to reach deeper cellular penetration. Additionally, concentrations of anti-ghrelin antibody needing to be injected for visualization of ghrelin-producing cells in the stomach may be so high that it is financially impractical for further testing at this time.

Budget:

SAGES RESEARCH GRANT APPLICATION
BUDGET SHEET

Detailed budget for 12 month period from 1/1/2014 through 12/31/2015.
Dollar amount requested (Omit cents): $30,000

NAME	POSITION TITLE	TIME/EFFORT		SALARY	FRINGE BENEFITS	SUB-TOTALS
		%	Hrs/ Week			
1. Bryan Sandler, MD	Principal Investigator*	5		[redacted]	[redacted]	[redacted]
2. Research Fellow - TBD	Study Coordinator	16		$6,282	1388	$7,670
3.						
4.						
5.						
CONSULTANT COSTS						
EQUIPMENT (List all Items&Total Equipment Cost)						
SUPPLIES (List all Items&Total Supplies Cost)	Mouse housing and food, operating equipment, mice, fluorescent labeling antibody, anti-ghrelin antibody					$21,000
TRAVEL**						$1,000
PATIENT CARE COSTS						$0
CONSORTIUM/CONTRACTUAL COSTS						$0
OTHER EXPENSES (List all Items & Total Cost)	NGN					$330
TOTAL DIRECT COSTS						$30,000

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Local/Institutional Review Board:
All animal studies are carried out according to protocols approved by IACUC Committee at the University of California San Diego. The University Division of Surgical Oncology within the Department of Surgery has an IACUC protocol which they use for immunofluorescent imaging of pancreatic tumors. We have created a unique IACUC protocol for imaging ghrelin cells in a mouse model using these immunofluorescent imaging techniques that will be submitted concurrently with this grant application.

Available Resources:

1. **University of California San Diego Health System,** along with UC San Diego School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences comprise UC San Diego Health Sciences, which over the past four decades has gained international recognition as a place where discoveries are delivered – bringing breakthroughs from the research lab bench to patients' bedsides. UC San Diego Health System is San Diego's only academic health system and is composed of UC San Diego Medical Center in Hillcrest, and UC San Diego Thornton Hospital, Moores Cancer Center, Shiley Eye Center, Sulpizio Cardiovascular Center and Jacobs Medical Center (opening in 2016) in La Jolla, as well as other primary and specialty practices of UC San Diego Medical Group located throughout southern California. Our dedicated doctors, surgeons, nurses, pharmacists, physician assistants, nurse practitioners, social workers, technicians and countless others provide compassionate, patient-centered care every day to patients from around the corner and around the world. The resources for creating a device registry of our own as well as using the NSQIP database are possible.
2. **The Center for the Future of Surgery (CFS)** is situated in the new Medical Education and Telemedicine (MET) Building. The building, constructed at a cost of $65 million, has 45,000 square feet and includes a research suite where physicians and scientists work together across disciplines and collaborate to deliver new discoveries. This facility offers the investigators a perfect opportunity to work in an environment planned from the ground up to ensure close coordination of clinical, research and educational endeavors.
3. **UCSD Vivarium** is situated on the medical school campus, near the CFS, and will be used as the location to perform our feasibility study. The vivarium is accredited and has all holding equipment, personnel, and operative enclosures needed to perform our experiment successfully. The IACUC requires this vivarium for the approved use during our experiment.

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Bryan J. Sandler, MD	Assistant Professor of Surgery
eRA COMMONS USER NAME bsandler	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Virginia	B.A.	1992-1996	Biology
Georgetown University	M.D.	1997-2001	Doctor of Medicine
Carolinas Medical Center	Internship	2001-2002	Surgery
Orlando Regional Healthcare	Residency	2002-2007	Surgery
University of California, San Diego	Fellowship	2007-2008	Minimally Invasive Surg

A. Personal Statement

The goal of the proposed research is to assess the feasibility of in vivo visualization of ghrelin production in a bariatric surgical mouse model. Immunofluorescence in surgery is presently being used to assess tumor margins in surgical oncology, bile and biliary anatomy in laparoscopic or robotic-assisted surgical procedures, and other surgical procedures. Here we intend to explore the feasibility of visualization of ghrelin-producing cell and cell mass within the gastric wall using immunofluorescence and photo-fluorescent imaging techniques. At UCSD in the Department of Surgery, we have a unique opportunity to explore photo-fluorescent imaging, as this is on-going research in the lab of one of my co-investigators, Dr. Micheal Bouvet, who has used photo-fluorescence to visualize tumor burden, margins, and tumor angiogenesis in an in vivo mouse model.

B. Positions and Honors

Positions and Employment

2007-2008 Clinical Instructor, Department of Surgery, University of California, San Diego
2009-present Assistant Professor, Department of Surgery, University of California, San Diego (UCSD)
2009-present Director of Bariatric Surgery, VA San Diego Healthcare System
2012-present Director of Surgical Endoscopic Education, Center for the Future of Surgery, Department of Surgery, University of California, San Diego

Other Experience and Professional Memberships

2002- present Member, American College of Surgeons
2006- present Member, Society of Gastrointestinal and Endoscopic Surgeons
2009-2012 Member, Minimally Invasive Robotic Association
2011- present Fellow, American College of Surgeons
2009- present Reviewer, Journal of Laparoendoscopic and Advanced Surgical Techniques
2010- present Reviewer, Surgical Endoscopy

Honors

2003 Best Research Paper and Presentation, 16th Annual Florida Vascular Society
2007 Best Resident Paper and Presentation, Southeastern Surgical Congress Annual Scientific Meeting
2007 Outstanding Academic Achievement and Service to the Organization, Orlando Regional Healthcare System
2012 Recognition of Excellence Award, Society of Gastrointestinal and Endoscopic Surgeons
2013 Recognition of Excellence Award, Society of Gastrointestinal and Endoscopic Surgeons

C. Selected Peer-reviewed Publications

Most relevant to the current application

1. Sandler BJ, Rumbaut R, Swain CP, Torres G, Morales L, Conzales L, Schultz S, Talamini M, Horgan S: *Human Experience with an Endoluminal, Endoscopic Gastrojejunal Bypass Sleeve.* Surg Endosc 2011 Sep;25(9):3028-33. Epub 2011 Apr 13.
2. Meireles O, Horgan S, Jacobsen GJ, Katagiri T, Sandler BJ, Dotai T, Mathew A, Sedrak M, Savides T, Nijhawan S, Majid S, Talamini M. *Transesophageal Endoscopic Myotomy (TEEM) for the Treatment of Achalasia – The United States human experience.* Surg Endosc 2013 May; 27 (5): 1803-9.
3. Horgan S, Meireles O, Jacobsen GJ, Sandler BJ, Ferreres A, Ramamoorthy S, Savides T, Katagiri T, Dotai T, Sedrak M, Majid S, Nijhawan S, Talamini M: *Broad Clinical Utilization of NOTES. Is it Safe?* Surg Endosc 2013 March 12 [Epub ahead of print]
4. Dotai T, Coker AM, Antozzi L, Acosta G, Michelotti M, Bildzukewicz N, Sandler BJ, Jacobsen GR, Talamini MA, Horgan S. *Transgastric large-organ extraction: the initial human experience.* Surg Endosc 2013 Feb; 27 (2): 394-399.
5. Jiang Y, Sandler B, Bhargava V, Mittal RK: *Antireflux action of Nissen fundoplication and stretch-sensitive mechanism of lower esophageal sphincter relaxation*. Gastroenterology. 2011 Feb; 140 (2): 442-9. Epub 2010 Oct 16.
6. Horgan S, Cullen JP, Talamini MA, Mintz Y, Ferreres A, Jacobsen GR, Sandler BJ, Bosia J, Savides T, Easter DW, Savu MK, Ramamoorthy SL, Whitcomb E, Agarwal S, Lukacz E, Dominguez G, Ferraina P: *Natural Orifice Surgery: Initial Clinical Experience.* Surg Endosc. 2009 Jul; 23(7): 1512-8. Epub 2009 Apr 3.
7. Horgan S, Cullen JP, Talamini MA, Mintz Y, Ferreres A, Jacobsen GR, Sandler BJ, Bosia J, Savides T, Easter DW, Savu MK, Ramamoorthy SL, Whitcomb E, Agarwal S, Lukacz E, Dominguez G, Ferraina P: *Natural Orifice Surgery: Initial Clinical Experience.* Surg Endosc. 2009 Jul; 23(7): 1512-8.
8. Nijhawan S, Barajas-Gamboa JS, Majid S, Jacobsen GR, Sedrak M, Sandler BJ, Talamini MA, Horgan S. *NOTES transvaginal hybrid cholecystectomy: the United States human experience.* Surg Endosc 2013 Feb; 27 (2): 514-517.
9. Cheverie J, Sandler BJ, Horgan S, Coker A, Barajas-Gamboa JS, Green S, Manuel V, Macias A, Talamini M, Grunvald E, Jacobsen GR. *Laparoscopic Sleeve Gastrectomy: An Efficacious Management of Metabolic Syndrome in the Morbidly Obese.* In Review – Surg Endosc
10. Jacobsen GR, Sandler BJ, Barajas-Gamboa JS, Coker A, Cheverie J, Macias A, Talamini M, Horgan S. *Trans-Vaginal Organ Extraction: Potential For Broad Clinical Application.* In Review – Surg Endosc
11. Sandler BJ, Rumbaut R, Swain CP, Torres G, Morales L, Conzales L, Schultz S, Talamini M, Horgan S: *One-year Human Experience with a Novel Endoluminal, Endoscopic Gastric Bypass Sleeve for Morbid Obesity.* In Review – Surg Endosc

D. Research Support

Active

NOSCAR Research Grant — 2010 – ongoing
$200,000

Prospective Multicenter Human Case Controlled Evaluation of Natural Orifice Translumenal Enodsocpic Surgery (NOTES) Cholecystectomy
Role: Co-investigator

Gore Research Grant (W.L. Gore & Associates) — 2011-2014
$55,000

Prospective, Multicenter, Observational Study to Evaluate Single-Staged Open Complex Ventral Incisional Hernia Repair Using a Bioabsorbable Material For Midline Fascial Closure Reinforcement

Role: Co-investigator

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Ryan C Broderick, MD	Postdoctoral Research Fellow
eRA COMMONS USER NAME (credential, e.g., agency login) rbroderick	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Cincinnati	BS	06/07	Biomedical Engineering
University of Cincinnati	MD	06/11	
University of California San Diego		07/11-06/13	General Surgery Categorical Resident
University of California San Diego		07/13-present	MIS Research Fellow

A. Personal Statement

The goal of my proposed research is to transform bariatric surgery by ultimately introducing a novel way of in vivo imaging of the gastric mucosa. If we are able to prove feasibility, cell-specific targeting could become a reality. With the help from Dr. Bouvet and Dr. Maawy's lab, we have the resources and knowledge to determine if this is a viable option. Due to the overall potential impact on a nationwide and global problem, it is with great motivation that I pursue this project.

B. Position and Honors

Positions and Employment

2004 Research and Development Engineer Intern; Medtronic, Inc; Galway, Ireland
2005-2006 Research and Development Engineer Co-op; Ethicon Endo Surgery, Inc; Cincinnati, OH
2008 Adjunct Gross Anatomy Faculty Member; College of Mount St. Joseph; Cincinnati, OH
2001-present Categorical General Surgery Resident; University of California San Diego; San Diego, CA
2013-present Research Fellow, Department of Minimally Invasive Surgery, University of California San Diego; San Diego, CA

Professional Membership

2004-2011 Student Member, Biomedical Engineering Society
2008-2011 Student Member, American College of Surgeons
2010-2012 Member, Alpha Omega Alpha Honor Society
2011-present Resident Member, American College of Surgeons
2013-present Candidate Member, Society of American Gastrointestinal and Endoscopic Surgeons

Honors

2007 Valedictorian, Biomedical Engineering, University of Cincinnati
2011 Best Physical Exam Skills Applied to Clinical Decision Making, University of Cincinnati COM
2013 Outstanding Resident Teacher Award, Department of Surgery, University of California San Diego

C. Selected Peer Reviewed Publications

N/A

BIOGRAPHICAL SKETCH

NAME Santiago Horgan, MD	POSITION TITLE Professor of Surgery
eRA COMMONS USER NAME (credential, e.g., agency login) shorgan	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Buenos Aires University - Medicine Faculty	MD	1984-1990	Medicine
Hospital de Clinicas, University of Buenos Aires		1991-1995	Surgery Residency
University of Washington Medical Center, Seattle		1995-1997	Clinical Fellowship
University of Illinois at Chicago	Assistant Professor	1999-2005	Surgery
	Associate Professor	2005-2006	Surgery
University of Illinois at Chicago	Professor of Surgery	2006-present	Minimally Invasive Surgery
University of California, San Diego			

A. Personal Statement

I am the Director of the Center for the Future of Surgery, chief of Minimally Invasive Surgery at UC San Diego Health System. I believe this grant is paramount in further understanding the ghrelin cells of the gastric mucosa. A cell-specific surgical approach, if possible, could be the next generation of bariatric surgery. Drs. Sandler, Broderick, Bouvet, and Maawy have the ability to complete this project on time and within budget.

B. Positions and Honors

Honors and Awards

1993 Annual Scholarship Medicine University, Buenos Aires, Argentina
1995 Roemmers Gold Medal Award—Liver Ischemia After Reperfusion in Pigs.
2001 Class Act Winner 2000 University of Illinois at Chicago
2001 Young Surgeon Award Surgical Society of the Alimentary Tract
2001 Research Award SAGES
2003 The Distinguished Robotic Surgeon Award-Pioneer in Evolution and Advancement of DaVinci General Surgery, From Intuitive Surgical Corp.
2005 Accesit Award for Best Paper Presentation: Lessons learned after 420 minimally invasive robotic assisted procedures. 76º Congreso Argentino de Cirugía 2005
2009 Health Care Champions Award. UC San Diego Medical Center
2010 Who's Who in America 2011(65th Edition)
2010 HealthLeaders Media. The 20 People Who Make Healthcare Better 2010
2011 San Diego Magazine: 50 People to Watch in 2012

Memberships in professional societies

1992 Argentinean Association of Surgery
1996 The Society for Surgery of the Alimentary Tract (SSAT)
1997 The Henry N. Harkins Surgical Society

2001 The Illinois Surgical Society
2001 The International Society for Diseases of the Esophagus.
2003 Honorary Member Peruvian Surgical Society
2002 Society of Laparoendoscopic Surgeons
2003 Society of American Gastrointestinal Endoscopic Surgeons (SAGES)
2003 The Chicago Society for Gastroenterology
2003 Association for Surgical Education (ASE)
2003 Honorary Member Guatemalan Surgical Society
2003 Warren H. Cole Society
2003 The Kansas City Surgical Society
2003 Honorary Member Peruvian Colorectal Surgical Society
2004 American Medical Association (AMA)
2004 Club Italo-Argentino di Chirurgia
2005 The Chicago Surgical Society
2006 Minimally Invasive Robotics Association(MIRA)
2007 The Tecnologico de Monterrey School of Medicine
2007 The Costa Rican Surgical Association
2010 Pacific Coast Surgical Association
2011 Society of Laparoendoscopic Surgeons (SLS)
2011 American College of Surgeons Fellowship (FACS)

C. Selected Peer-reviewed Publications

Jacobsen GR, Barajas-Gamboa JS, Coker AM, Cheverie J, Macias CA, Sandler BJ, Talamini MA, Horgan S. Transvaginal organ extraction: potential for broad clinical application. Surg Endosc. 2013 Oct 23. [Epub ahead of print] PubMed PMID: 24149847.

Shah A, Boettcher E, Fahmy M, Savides T, Horgan S, Jacobsen GR, Sandler BJ, Sedrak M, Kalmaz D. Screening pre-bariatric surgery patients for esophageal disease with esophageal capsule endoscopy. World J Gastroenterol. 2013 Oct 7;19(37):6188-92. doi: 10.3748/wjg.v19.i37.6188. PubMed PMID: 24115815; PubMed Central PMCID: PMC3787348.

Meireles OR, Horgan S, Jacobsen GR, Katagiri T, Mathew A, Sedrak M, Sandler BJ, Dotai T, Savides TJ, Majid SF, Nijhawan S, Talamini MA. Transesophageal endoscopic myotomy (TEEM) for the treatment of achalasia: the United States human experience. Surg Endosc. 2013 May;27(5):1803-9. doi: 10.1007/s00464-012-2666-9. Epub 2013 Mar 23. PubMed PMID: 23525881.

McLemore EC, Coker AM, Devaraj B, Chakedis J, Maawy A, Inui T, Talamini MA, Horgan S, Peterson MR, Sylla P, Ramamoorthy S. TAMIS-assisted laparoscopic low anterior resection with total mesorectal excision in a cadaveric series. Surg Endosc. 2013 Sep;27(9):3478-84. doi: 10.1007/s00464-013-2889-4. Epub 2013 Mar 14. PubMed PMID: 23494511.

Horgan S, Meireles OR, Jacobsen GR, Sandler BJ, Ferreres A, Ramamoorthy S, Savides T, Katagiri T, Dotai T, Sedrak M, Majid SF, Nijhawan S, Talamini MA. Broad clinical utilization of NOTES: is it safe? Surg Endosc. 2013 Jun;27(6):1872-80. doi: 10.1007/s00464-012-2736-z. Epub 2013 Mar 12. PubMed PMID: 23479251.

Ganz RA, Peters JH, Horgan S, Bemelman WA, Dunst CM, Edmundowicz SA, Lipham JC, Luketich JD, Melvin WS, Oelschlager BK, Schlack-Haerer SC, Smith CD, Smith CC, Dunn D, Taiganides PA. Esophageal sphincter device for gastroesophageal reflux disease. N Engl J Med. 2013 Feb 21;368(8):719-27. doi: 10.1056/NEJMoa1205544. PubMed PMID: 23425164.

Jacobsen GR, Coker AM, Acosta G, Talamini MA, Savides TJ, Horgan S. Initial experience with an innovative endoscopic clipping system. Surg Technol Int. 2012 Dec;22:39-43. PubMed PMID: 23225590.

McLemore EC, Coker A, Jacobsen G, Talamini MA, Horgan S. eTAMIS: endoscopic visualization for transanal minimally invasive surgery. Surg Endosc. 2013 May;27(5):1842-5. doi: 10.1007/s00464-012-2652-2. Epub 2012 Nov 21. PubMed PMID: 23179071.

Dotai T, Coker AM, Antozzi L, Acosta G, Michelotti M, Bildzukewicz N, Sandler BJ, Jacobsen GR, Talamini MA, Horgan S. Transgastric large-organ extraction: the initial human experience. Surg Endosc. 2013 Feb;27(2):394-9. doi: 10.1007/s00464-012-2473-3. Epub 2012 Jul 18. PubMed PMID: 22806531.

Nijhawan S, Barajas-Gamboa JS, Majid S, Jacobsen GR, Sedrak MF, Sandler BJ, Talamini MA, Horgan S. NOTES transvaginal hybrid cholecystectomy: the United States human experience. Surg Endosc. 2013 Feb;27(2):514-7. doi: 10.1007/s00464-012-2470-6. Epub 2012 Jul 18. PubMed PMID: 22806528.

Sandler BJ, Rumbaut R, Swain CP, Torres G, Morales L, Gonzales L, Schultz S, Talamini M, Horgan S. Human experience with an endoluminal, endoscopic, gastrojejunal bypass sleeve. Surg Endosc. 2011 Sep;25(9):3028-33. doi: 10.1007/s00464-011-1665-6. Epub 2011 Apr 13. PubMed PMID: 21487876.

D. Research Support

Ongoing:

2004-2007 Ethicon Endo-Surgery, Inc.
Distance Learning in Minimally Invasive Surgery
$ 1,100,000, P.I.

2004-2007 Intuitive Surgical
Development of Robotic Surgery advance training programs
$ 1,2000,000. P.I.

2004-2007 Inamed
Center of excellence in the treatment of morbid obesity
Training center for Lap-band Surgery
$ 200,000

2007-2012 Allergan
Laparoscopic Adjustable Gastric banding (Lap-Band) as a Treatment for
Morbid Obesity in Adolescents LBA-001
850,000$

2007-2012 Allergan
EasyBand GOAL Trial: Gastric Banding System in Morbidly Obese Patients to Achieve Weightloss Protocol# 10042
$1,000,000

2007 AUGS (American Urogynecologic Society) Research Grant
A Prospective Cohort Study of the Impact of Surgically-Induced Weight Loss on Pelvic Floor Disorders
$24,000

2008-2009 USGI Research Grant
Intraluminal Gastric Reduction as Primary Therapy for Morbid Obesity ROSE Study $250,000

2008-2009 Medigus
Assessment of the Safety and Effectiveness of the SRS Endoscopic Stapling System
$303,898.00

2008-2009 USGI Research Grant
Gastric Restriction Using the EndoSurgical Operating System (EOS) POSE Study
$200,000

2008-2014 Torax Research Grant
LINX' Reflux Management System
$750,000

2009-2011 Ethicon Endosurgery Research Grant
A trial to evaluate Natural Orifice Transgastric Endoscopic Cholecystectomy
with laparoscopic assistance
$250,000

2010-2012 NOSCAR Research Grant
Prospective Multicenter Human Case Controlled Evaluation of Natural Orifice
Translumenal Enodsocpic Surgery (NOTES) Cholecystectomy
$200,000

Completed:

Funding Agency: NIH-FIRCA
Funding Period: January 1, 2001-December 31, 2004
Title: Mechanisms of Disease in Endometriosis
PI: Horgan
Role: PI
Goal: The major goal of this project is to identify the mechanisms of disease in endometriosis.

Funding Agency: Ethicon Endo-Surgery, Inc.
Funding Period: January 1, 2001-December 31,2004
Title: Surgical Education Curriculum Development
PI: Horgan
Role: PI
Goal: The major goal of this project is to advance the curriculum development in surgical education.

Funding Agency: Ethicon Endo-Surgery, Inc.
Funding Period: January 1, 2004-December 31,2006
Title: Surgical Education Curriculum Development
PI: Horgan
Role: PI
Goal: The major goal of this project is to advance the curriculum development in surgical education.

Funding Agency: Allergan Medical
Funding Period: January 1, 2005-December 31,2007
Title: FDA trial: Lap Band for the treatment of Obesity on Adolescents
PI: Horgan
Role: PI
Goal: The major goal of this project is to evaluate the safety and effectiveness of the LAP-BAND® System

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Michael Bouvet, M.D.	Professor of Surgery
eRA COMMONS USER NAME mbouvet	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Washington, Seattle, WA	BS	1981-1985	Microbiology
University of Washington, Seattle, WA	MD	1985-1989	Medicine
University of California San Diego, San Diego, CA	Residency	1989-1995	Surgery
MD Anderson Cancer Center, Houston, TX	Fellowship	1995-1998	Surgical Oncology

A. Personal Statement

For this grant application with Dr Sandler, I will provide my expertise in fluorescence imaging in mouse models. My laboratory has been involved in the development and preclinical application of clinically-relevant, metastatic orthotopic mouse models of pancreatic cancer made imageable with genetic reporters. These models utilize the human pancreatic cancer cell lines which have been genetically engineered to selectively express high levels of green fluorescent protein (GFP) or red fluorescent protein (RFP). Tumors with fluorescent genetic reporters are established subcutaneously in nude mice, and fragments of the subcutaneous tumors are then surgically transplanted onto the pancreas. Locoregional tumor growth and distant metastasis of these orthotopic implants occurs spontaneously and rapidly throughout the abdomen in a manner consistent with clinical human disease. Highly specific, high-resolution, real-time quantitative fluorescence imaging of tumor growth and metastasis may be achieved *in vivo* without the need for contrast agents, invasive techniques, or expensive imaging equipment. We have shown a high correlation between fluorescence optical imaging, magnetic resonance imaging, and ultrasound in these models. Such *in vivo* models have enabled us to visualize in real time and acquire images of the progression of pancreatic cancer in the live animal, and to demonstrate the real-time antitumor and antimetastatic effects of several novel therapeutic strategies on pancreatic malignancy. My lab has also developed and validated the use of fluorophore-conjugated antibodies for surgical navigation and laparoscopic localization of gastrointestinal tumors.

B. Positions and Honors

Positions and Employement

1998 to 2002 Assistant Professor of Surgery, University of California San Diego
1998 to present Director of Surgical Oncology and Endocrine Surgery, VA San Diego Healthcare System
2002 to 2006 Associate Professor of Surgery, University of California San Diego
2002 to present Co-Director, Moores UCSD Cancer Center Specialized Cancer Unit for GI Cancer
2005 to present Director, Endocrine Surgery, University of California San Diego
2006 to present Professor of Surgery, University of California San Diego

Other Experience and Professional Memberships

2001 to present Fellow, American College of Surgeons
2004 to present Editorial Board, *Annals of Surgical Oncology*, *Hepatogastroenterology*
2005 to 2011 Member, American Cancer Society Clinical Cancer Research & Epidemiology Study Section
2006 to 2012 Member, NCI Study Section, Subcommittee J, Population and Patient-Oriented Training
2009 to present Ad Hoc Member, NIH Clinical Studies Special Emphasis Panel Study Section
2010 to present Pancreatic Cancer Action Network-AACR Innovative Grants Scientific Review Committee

Honors

1998 The Lotzová Memorial Research Prize, M.D. Anderson Cancer Center

2012	UCSD Department of Surgery Faculty Research Award
2004-2013	Selected as one of "America's Top Surgeons" by the Consumers' Research Council of America
2008-2013	Selected as one of the Top Doctors of San Diego by the San Diego County Medical Society

C. Selected peer-reviewed publications (from 178 original articles).

1. **Bouvet M**, Tsuji K, Yang M, Jiang P, Moossa AR, Hoffman RM. In vivo color-coded imaging of the interaction of colon cancer cells and splenocytes in the formation of liver metastases. Cancer Research 66(23):11293-7, 2006. PMID: 17145875

2. Kaushal S, McElroy M, Luiken GA, Talamini MA, Moossa AR, Hoffman RM, **Bouvet M.** Fluorophore-conjugated anti-CEA antibody for the intraoperative imaging of pancreatic and colorectal cancer. Journal of Gastrointestinal Surgery 12(11):1938-1950, 2008. PMID: 18665430

3. Yang M, Reynoso J, Bouvet M, Hoffman RM. A transgenic red fluorescent protein-expressing nude mouse for color-coded imaging of the tumor microenvironment. J Cell Biochem 106(2):279-84, 2009. PMID: 19097136

4. Tran Cao HS, **Bouvet M**, Kaushal S, Keleman A, Romney E, Kim G, Fruehauf J, Imagawa DK, Hoffman RM, Katz MH. Metronomic gemcitabine in combination with sunitinib inhibits multisite metastasis and increases survival in an orthotopic model of pancreatic cancer. Mol Cancer Ther 9(7):2068-78, 2010. PMID: 20606044

5. Tran Cao HS, Kaushal S, Snyder CS, Ongkeko WM, Hoffman RM, **Bouvet M.** Real-time imaging of tumor progression in a fluorescent orthotopic mouse model of thyroid cancer. Anticancer Res. 30(11):4415-22, 2010. PMID: 21115887

6. Tran Cao HS, McElroy M, Kaushal S, Hoffman RM, **Bouvet M.** Imaging of the interaction of cancer cells and the lymphatic system. Adv Drug Deliv Rev. 63(10-11):886-9, 2011. PMID: 21718727

7. Tran Cao HS, Kaushal S, Lee C, Snyder CS, Thompson KJ, Horgan S, Talamini MA, Hoffman RM, **Bouvet M.** Fluorescence laparoscopy imaging of pancreatic tumor progression in an orthotopic mouse model. Surgical Endoscopy 25(1):48-54, 2011. PMID: 20533064

8. Tran Cao HS, Kaushal S, Menen RS, Metildi CA, Lee C, Snyder CS, Talamini MA, Hoffman RM, **Bouvet M**. Submillimeter-resolution fluorescence laparoscopy of pancreatic cancer in a carcinomatosis mouse model visualizes metastases not seen with standard laparoscopy. J Laparoendosc Adv Surg Tech A. 21(6): 485-489.2011. PMID: 21699431

9. **Bouvet M,** Hoffman RM. Glowing tumors make for better detection and resection. Sci Transl Med. 3(110):110fs10, 2011. PMID: 22116932

10. Suetsugu A, Katz M, Fleming J, Truty M, Thomas R, Moriwaki H, **Bouvet M,** Saji S, Hoffman RM. Multi-color palette of fluorescent proteins for imaging the tumor microenvironment of orthotopic tumorgraft mouse models of clinical pancreatic cancer specimens. J Cell Biochem. 113(7):2290-5, 2012. PMID: 22573550

11. Menen RS, Hassanein MK, Momiyama M, Suetsugu A, Moossa AR, Hoffman RM, **Bouvet M.** Tumor-educated macrophages promote tumor growth and peritoneal metastasis in an orthotopic nude mouse model of human pancreatic cancer. In Vivo. Jul;26(4):565-9, 2012. PMID: 22773569

12. Grzesiak JJ, Cao HS, Burton DW, Kaushal S, Vargas F, Clopton P, Snyder CS, Deftos LJ, Hoffman RM, **Bouvet M.** Knockdown of the β(1) integrin subunit reduces primary tumor growth and inhibits pancreatic cancer metastasis. Int J Cancer. 129(12):2905-15, 2011. PMID: 21491421

13. Metildi CA, Kaushal S, Hardamon CR, Snyder CS, Pu M, Messer KS, Talamini MA, Hoffman RM, **Bouvet M**. Fluorescence-guided surgery allows for more complete resection of pancreatic cancer, resulting in longer disease-free survival compared with standard surgery in orthotopic mouse models. J Am Coll Surg. 215(1):126-35; discussion 135-6, 2012. PMID: 22632917

14. Metildi CA, Kaushal S, Lee C, Hardamon CR, Snyder CS, Luiken GA, Talamini MA, Hoffman RM, **Bouvet M**. An LED light source and novel fluorophore combinations improve fluorescence laparoscopic detection of metastatic pancreatic cancer in orthotopic mouse models. J Am Coll Surg. 2012 214(6):997-1007. PMID: 22542065

15. Snyder CS, Harrington AR, Kaushal S, Mose E, Lowy AM, Hoffman RM, **Bouvet M**. A dual color, genetically engineered mouse model for multi-spectral imaging of the pancreatic microenvironment. Pancreas 42(6):952-8, 2013. PMID: 23648841

D. Research Support

Ongoing Research Support

NIH National Cancer Institute Bouvet (PI) 01/01/09 – 12/31/2013
1R01CA132971-01A1
"Color-Coded Imaging of Pancreatic Cancer Microenvironment for Drug Discovery"
The major goals of this project are to color-code the pancreatic cancer microenvironment for drug discovery.
Role: Principal Investigator

NIH National Cancer Institute Bouvet (PI) 06/24/10 – 04/30/15
1R01CA142669-01A1
"Fluorophore-Conjugated Antibodies for Imaging and Resection of GI Tumors"
The major goals of this project are to develop and validate fluorophore conjugated antibodies for imaging and resection of gastrointestinal tumors.
Role: Principal Investigator

NIH/NHLBI Fuster (PI)
07/01/12 - 06/30/16
R01 HL107652-01
"Lymphatic Microenvironment: Altering Cell Traffic by Targeting Glycans"
The major goals for this proposal are: (1) Assess the effects of genetically altering lymphatic endothelial heparan sulfate on experimental cell trafficking to regional lymph nodes in vivo. (2) Determine the specific role of heparan sulfate in establishing lymphatic chemokine gradients. (3) Characterize the importance of lymphatic endothelial heparan sulfate as a co-receptor for chemokine-dependent cell migration and signaling in the lymphatic microenvironment.
Role: Co-Investigator

Recently Completed Research Support

NIH/NCI Doran/Bouvet (Co-Leaders) 5/23/13 – 8/31/13
U54CA132384 and U54CA132379
"Analysis of Oral Microbiota in Human Subjects".
SDSU-UCSD Cancer Center Partnership U54 Pilot Project

The major goals of this project are to characterize the oral microbiota of patients with pancreatic and other digestive cancers compared to healthy controls by prospectively enrolling patients from the UCSD Medical Center.
Role: Co-Leader

NIH National Cancer Institute Cheresh (PI) 06/01/07 – 5/31/12
2R01CA045726-21A1
"Regulation of metastasis by alpha V integrin and Src"
The major goals of this grant are to study the regulation of metastasis by alpha V integrin and src.
Role: Co-Investigator

UCSD Moores Cancer Center Klemke/Bouvet (Co-PIs) 4/15/11 – 4/14/12
Translational Cancer Research Award
"Analysis of PEAK1 Tyrosine Kinase as a Diagnostic and Predictive Biomarker in Pancreatic Cancer"
The major goals of this project are to analyze PEAK1 as a biomarker in pancreatic cancer.
Role: Co-PI

VA Merit Review Bouvet (PI) 04/01/08 – 03/31/12
"Tumor-stroma interactions in pancreatic cancer"
The major goals of this project are to characterize tumor stroma interactions in pancreatic cancer.
Role: Principal Investigator

NIH National Cancer Institute Bouvet (PI) 03/01/09 – 02/28/11
1R21CA135435-01A1
"Divalent cation activation of the integrin-mediated malignant phenotype in pancreatic cancer."
The major goals of this project are to determine the effects of altered divalent cations on the integrin-mediated malignant phenotype in our in vivo mouse models of pancreatic cancer.
Role: Principal Investigator

1U54CA119335-01 Esener (PI) 09/30/05 – 08/31/10

NIH/NCI
"Centers of Cancer Nanotechnology Excellence"
The major goals of this project are to perfect a practical nanotechnology base to diagnose, treat, and monitor cancers.
Role: Co-Investigator in Imaging and Animal Core

NIH National Cancer Institute Bouvet (PI) 09/01/07 – 08/31/09
R33CA109949-03
"Imageable mouse models of pancreatic cancer"
The major goals of this project are to develop novel mouse models of pancreatic cancer from tumor specimens.
Role: Principal Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Ali A. Maawy, MD	Postdoctoral Research Fellow
eRA COMMONS USER NAME (credential, e.g., agency login) amaawy	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Nairobi		08/98 - 09/00	Medicine
Richland College		06/01 – 08/04	Pre-medicine
University of Texas Dallas		08/04 – 08/05	Neuroscience
University of Texas Southwestern Medical School	MD	08/05 – 06/09	Medicine
University of California San Diego		07/09-06/12	General Surgery Categorical Resident
University of California San Diego		07/12-present	Research Fellow

D. Personal Statement

I am currently a research resident in the department of surgical oncology and I'm keenly interested in the study of pancreatic cancer, optics, photonics and the development of fluorescence guided surgery. To this aim, we hope to advance the field of fluorescence guided surgery in the developing of novel imaging techniques with both open and laparoscopic surgery. Specifically, we hope to evaluate metabolic surgery and the understanding the role of ghrelin in the overall outcomes of surgery. In addition we hope to improve surgical techniques by evaluating the required extent of resection guided by fluorescent imaging and assessing ghrelin distribution.

Positions and Honors

Positions and Employement

1999 to 2000 Department of Anatomy Teaching Assistant, University of Nairobi
2001 to 2005 Assembler and Quality Technician, Fork lift operator 1998 to 2002, Flextronics International, Dallas Tx
2004 Princeton Review Instructor
2006 to 2009 Teaching Assistant, Department of Anatomy, UT Southwestern School of Medicine
2009 to present Resident in the Department of Surgery, UCSD Medical Center

Other Experience and Professional Memberships

2005 – 2009 Student National Medical Association
2006 to present Member, American Medical Association
2010 to present Member, American College of Surgeons
2012 to present Association for Academic Surgery
2012 to present American Association for Cancer Research

Awards and Honors

2003 Outstanding Student in Math Science, and Engineering, at Richland College
2005 McGraw Hill 205 Lange Student Award for outstanding academic achievements
2005 Belkin scholar and scholarship
2007 Highest medical licensing exam score ever attained, UT Southwestern
2013 Best research poster presentation, UCSD Surgery Research Symposium

E. Selected Peer Reviewed Publications

McLemore EC, Coker AM, Devaraj B, Chakedis J, Maawy A, Inui T, Talamini MA, Horgan S, Peterson MR, Sylla P, Ramamoorthy S. **TAMIS-assisted laparoscopic low anterior resection with total mesorectal excision in a cadaveric series**. Surg Endosc 2013 Mar 14.

Hiroshima Y, Zhao M, Zhang Y, Maawy A, Hassanein MK, Uehara F, Miwa S, Yano S, Momiyama M, Suetsugu A, Chishima T, Tanaka K, Bouvet M, Endo I, Hoffman RM. **Comparison of efficacy of Salmonella typhimurium A1-R and chemotherapy on stem-like and non-stem human pancreatic cancer cells.** Cell Cycle. 2013 Aug 6;12(17).

Ali A Maawy, Yukihiko Hiroshima, Sharmeela Kaushal, George A. Luiken, Robert Hoffman, Michael Bouvet. **Comparison of a chimeric anti-CEA antibody conjugated with visible or near infrared fluorescent dyes for imaging pancreatic cancer in orthotopic nude mouse models.** - Accepted for publication, Journal of Biomedical Optics

BIOGRAPHICAL SKETCH

NAME Moneer E. Almadani, MD PhD	POSITION TITLE Research Fellow
eRA COMMONS USER NAME Malmadani	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
King Khalid University, Abha-Saudi Arabia	MD	06/2004	Medicine
King Fahad National Guard Hospital, Riyadh-Saudi Arabia		07/2005	Internship
King Faisal Specialist Hospital,& Research Center, Riyadh- Saudi Arabia		09/2010	Surgery Residency
King Faisal Specialist Hospital,& Research Center, Riyadh- Saudi Arabia		12/2012	Minimally Invasive Surgery
Alfaisal University, Riyadh- Saudi Arabia		01/2012	Senior Lecturer
Alyamamh Hospital, Ministry Of Health, Riyadh- Saudi Arabia		07/2012	Surgical Specialist
Alyamamh Hospital, Ministry Of Health, Riyadh- Saudi Arabia		10/2012 - present	Senior Specialist
University of California, San Diego, Dept of Surgery		06/2013 – present	Research Fellow, Minimally Invasive Surgery

A. Personal Statement

The propose goal of this study is to prove the feasibility of labeling mouse stomach cells with an injectable anti-ghrelin antibody, and visualize gastric ghrelin cells in vivo using a special Digital camera that introduced through a surgical stomach incision under general anesthesia.

I have the intent, & the experience needed to help Dr. Sandler, & successfully, carry out this important project. I am familiar, & having the necessary experience to conduct a surgical feasibility research, through my previous work at one of the biggest tertiary care centers in the middle east, King Faisal Specialist Hospital & Research Centre KFSH&RC.

I am motivated by this animal model, because of its potential impact, giving some tips for understanding the idea behind the long-term success of some bariatric procedures, & their relation to Ghrelin cells. If proven, then it will be implemented clinically to be applied in humans by allowing for direct visualization of ghrelin producing cells intraoperatively which could target the therapy for sleeve gastrectomy, & Endoscopic bariatric procedures, which in turn is very important at the level of future surgical improvement and outcome.

In summary, I have an important hot topic in metabolic surgical research. My skills, & experience have prepared me to assist Dr. Sandler in this feasibility study.

B. Positions and Honors

Positions and Employment

10/2005-09/2010	Surgical Resident, Department of Surgery, King Faisal Specialist Hospital & Research Centre, Riyadh- Saudi Arabia
04/2009-03/2010	Chief resident at King Faisal Specialist Hospital and Research Centre- Riyadh, KSA, Department of surgery
04/2009-03/2010	Member of at Morbidity & Mortality committee, King Faisal Specialist Hospital and Research Centre-Riyadh , KSA, Department of surgery
04/2009-03/2010	Coordinator of Pathology, & Radiology meetings of the academic resident's activity at King Faisal Specialist Hospital and Research Centre- Riyadh , KSA,
01/2012-present	Senior lecturer, Alfaisal University, Riyadh- Saudi Arabia
11/2010-07/2012	Fellow, Minimally Invasive Surgery, King Faisal Specialist Hospital and Research Centre, Riyadh- Saudi Arabia
10/2012-11/2012	Specialist, Department of Surgery Alyamamah hospital, Ministry of Health, Riyadh- KSA
12/2012-Present	Senior Specialist, Department of Surgery Alyamamah hospital, Ministry of Health, Riyadh- KSA
06/2013-present	Research Fellow, Department of Surgery, University of California, San Diego (UCSD)

Honors

2005	Best Junior Resident Award at the Laparoscopic and Robotics Workshop, King Faisal Specialist Hospital & Research Centre, Riyadh- Saudi Arabia
2012	Letter of appreciation for the outstanding achievement in academic teaching- Alfaisal University, Riyadh- Saudi Arabia

Professional Registration,& Membership

2005 – 2010	Resident member, Saudi Commission for Health Specialties SCFHS 2010-present
	Specialist member, Saudi Commission for Health Specialties SCFHS 2013 –
present	Member, Society of American Gastrointestinal and Endoscopic Surgeons

C. Selected Peer-reviewed researches:

- **Laparoscopic Redo sleeve gastrectomy feasibility and early outcome**, (Moneer AL-Madani MD, Fahad Bamehriz MD, A. Salem MD, P O'Regan MD)
- **Adrenalectomy For Pheochromocytoma In The Era Of Laparoscopic Surgery** (M. Al Madani MD, H. Al Mutairi MD, S. Alsobhi MD)
- **The Value of Stress Thallium as a Preoperative Cardiac Evaluation Tool for Vascular Procedures**
(Moneer AL-Madani MD, Bassel Safi MD)
- **Acceptability of a pathway Implementation Format by Medical staff of King Fahad National Guard Hospital', Riyadh**
(Moneer AL-Madani MD, Nabil Ismail MD, Imad Hassan MD)

Participation in SAGES:

Bryan Sandler, MD is a member of SAGES and active on several committees, including the Technology Assessment and Value committee and the Flexible Endoscopy committee. He has served as Equipment Czar at the Annual meeting in 2012, has run several of the Hands-on Courses at the annual meetings and has also been the course chair for the annual Fellows Course, held in 2013 in San Diego. He has written or co-authored many abstracts and manuscripts submitted to both the SAGES annual meeting as well as to Surgical Endoscopy.

Santiago Horgan, MD is a member of SAGES and member of the Board of Directors of SAGES. He has been a past program chair for the annual SAGES *meeting* in 2012. He supports many abstracts and manuscripts submitted to both SAGES and Surgical Endoscopy.

Ryan C Broderick, MD is a candidate member of SAGES. He has submitted multiple abstracts for presentation during the 2014 annual meeting.

Micheal Bouvet, MD is a member of SAGES. He has submitted multiple abstracts and manuscripts to both SAGES and Surgical Endoscopy.

Moneer Almadani, MD is a candidate member of SAGES. She has submitted multiple abstracts for presentation during the 2014 annual meeting.

Ali Maawy, MD is not a member of SAGES.

Appendix:
Below are the images referenced in the Background section for further clarification on our intended imaging technique.

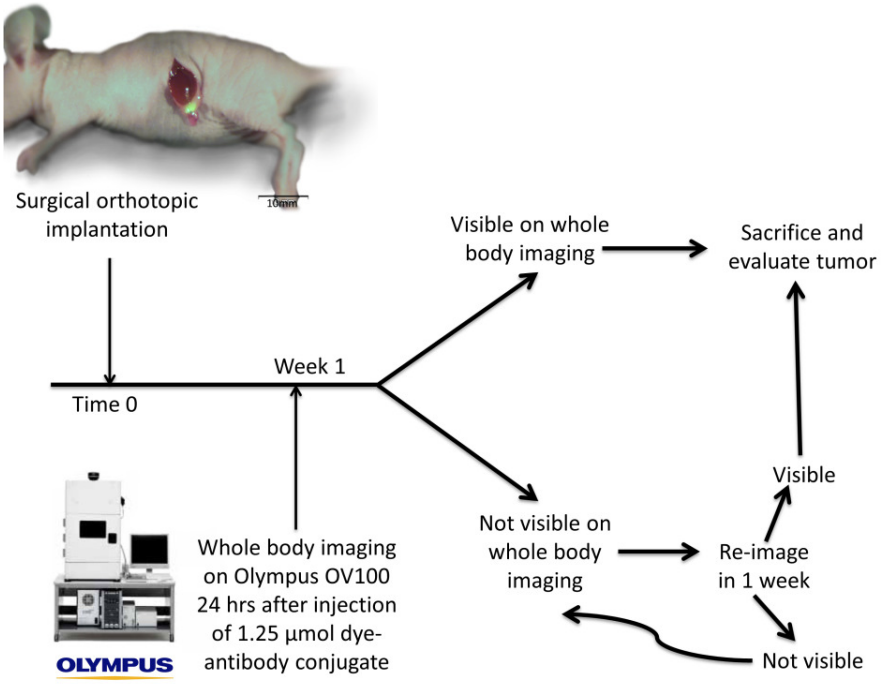

Figure 1 Illustration of experimental plan for pancreatic tumor visualization. Serial weekly imaging is designed to attempt to capture the smallest visible tumor on whole body imaging.

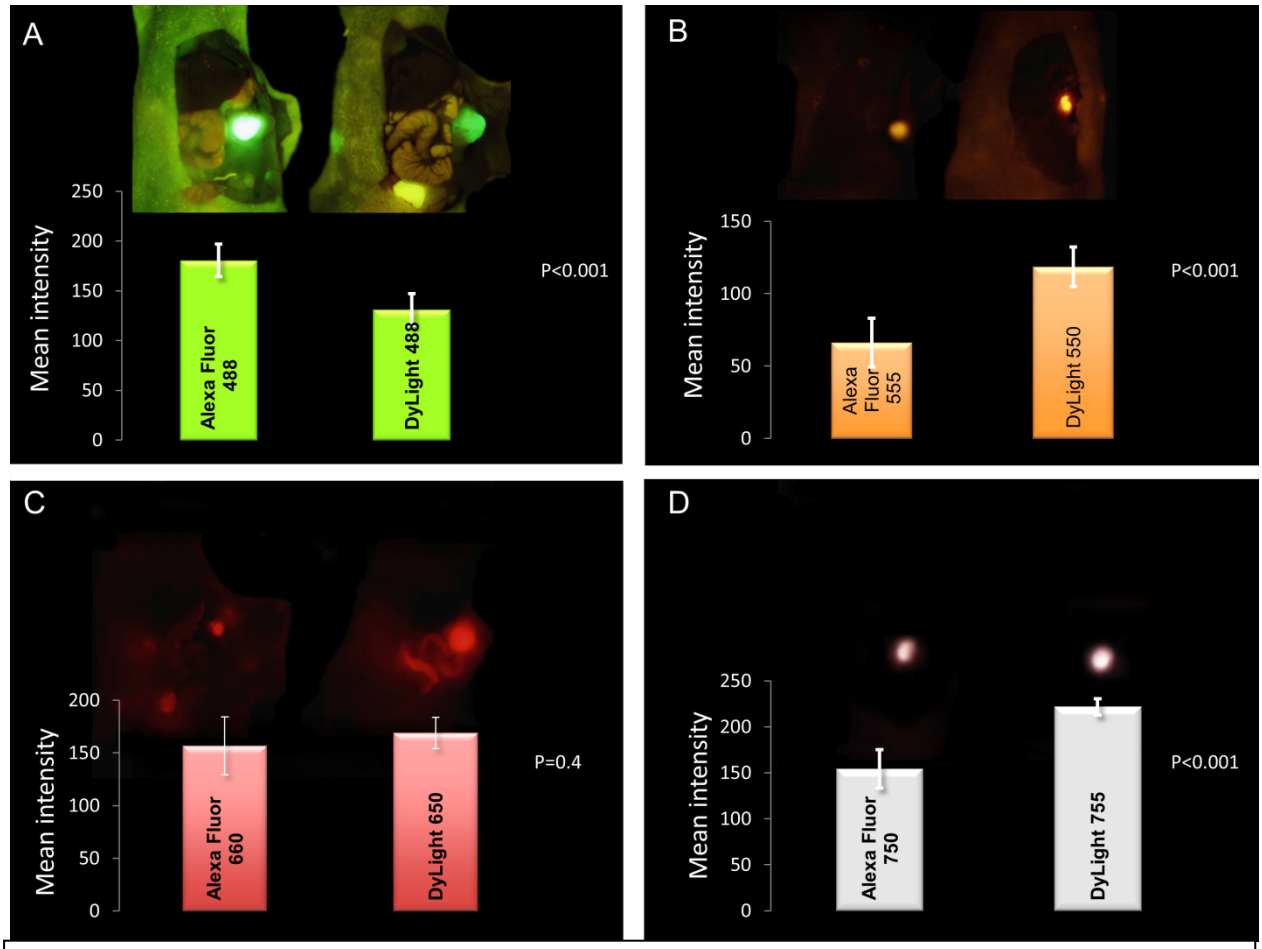

Figure 2 Representative images of each dye used in imaging studies. A: Alexa Fluor 488 is significantly brighter than DyLight488 ($p<0.001$). B: DyLight 550 is significantly brighter than Alexa Fluor 555 ($p<0.001$). C: Although DyLight 650 appeared brighter, no significant difference was noted between Alexa Fluor 660 and DyLight 650 ($p=0.4$). D: DyLight755 is significantly brighter than Alexa Fluor 750 ($p<0.001$). Note the decreasing ability to discern the background with increasing wavelength (A-D).

Fluorescence laparoscopy. We have developed fluorescence laparoscopy in mouse models to image pancreatic tumors and their metastases using small laparoscopes with appropriate filters (Figure 3). This technology allows for a minimally-invasive approach to monitoring of tumor growth in response to novel anti-tumor and anti-stromal therapies. A similar approach could be used to image ghrelin expressing cells in the stomach.

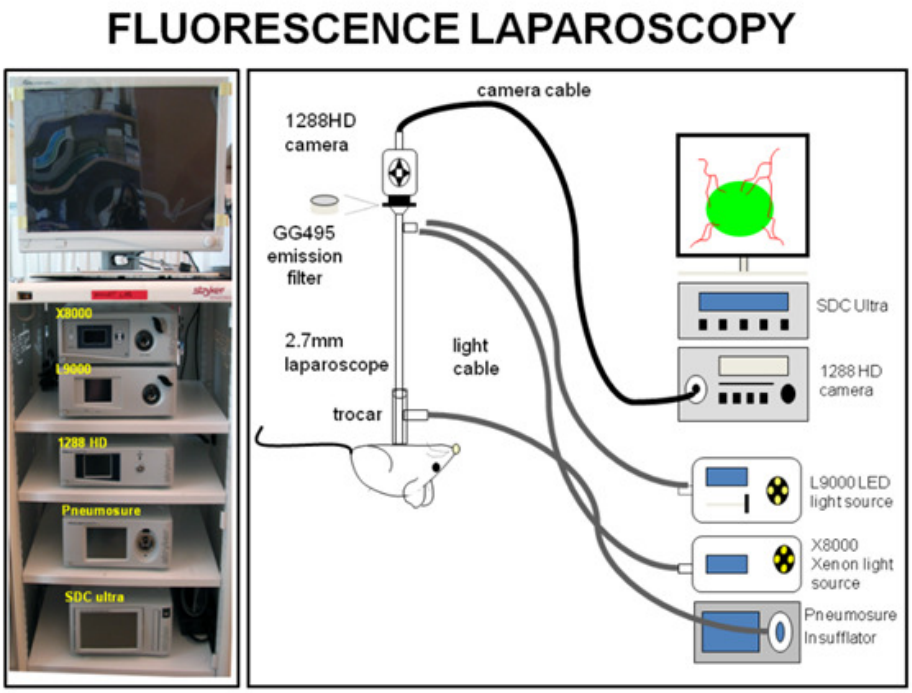

Figure 3. Customized fluorescence laparoscopy. A standard laparoscopic tower was modified to achieve a fluorescence light mode that would permit detection of fluorescence signals while still allowing visualization of the non-fluorescent background tissue. The LED light source (Stryker L9000 LED lamp) was filtered through a glass emission filter (Schott GG495) that was placed between the laparoscope and the 1288 HD camera. With alterations to red, blue and green components of the LED light source, tumors of different fluorescence wavelengths were simultaneously visualized. A Stryker X8000 xenon light source was used for bright field laparoscopy.

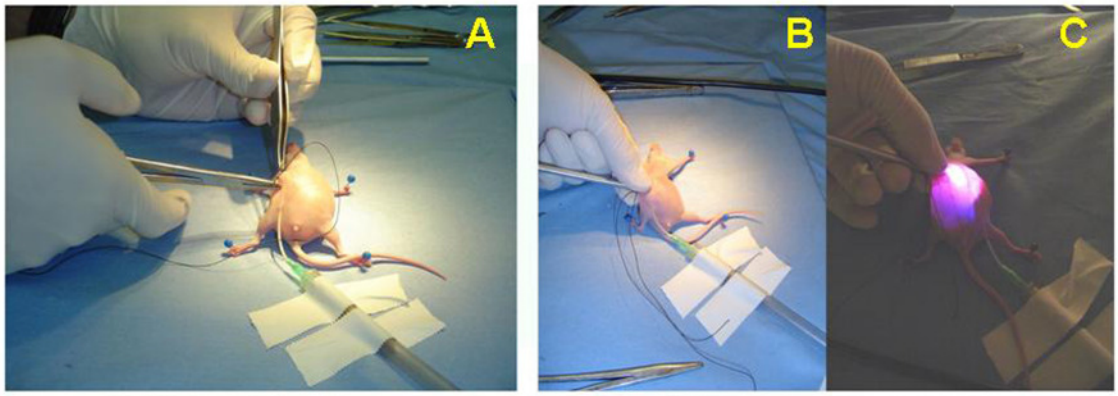

Figure 4. Fluorescence laparoscopy. Once anesthetized, the mouse's abdomen was insufflated (A). A laparoscope was inserted to visualize the abdominal cavity (B). Fluorescence was excited by a LED blue light (C)

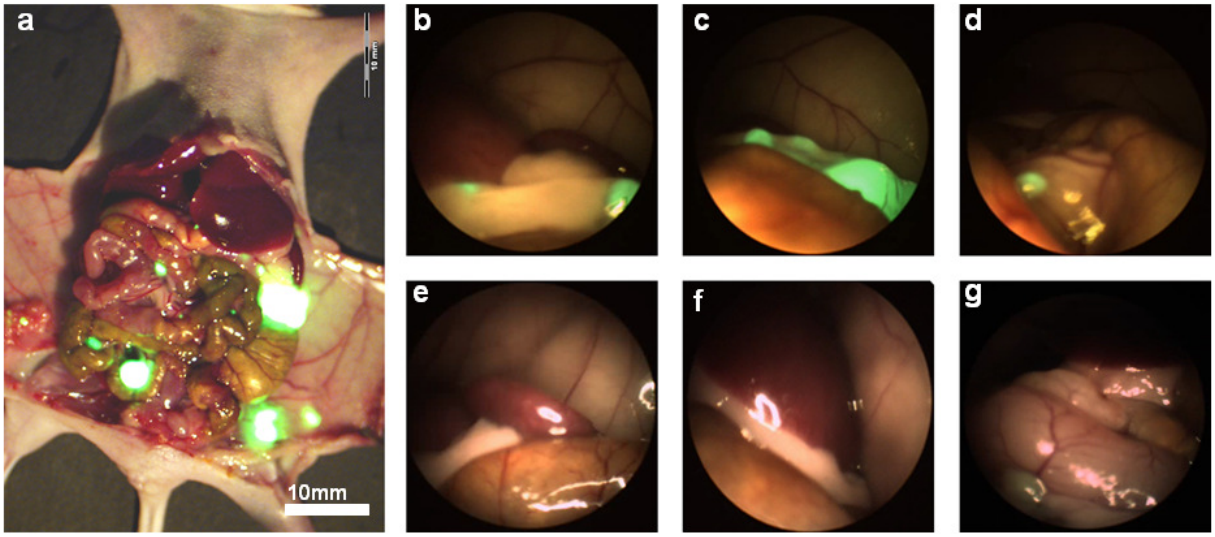

Figure 5: Comparative identification of metastases under brightfield and fluorescence laparoscopy. a) OV-100 open image from a representative mouse. View of left upper quadrant in a mouse specimen under FL (b-d) and BL (e-g). While the green fluorescence of the metastatic lesion was unmistakable under FL, under BL lesions resembled normal tissue and were not identifiable as metastases.