THE 40TH ANNUAL FITZ-HUGH SYMPOSIUM

RESIDENT RESEARCH PRESENTATIONS

Thursday June 23, 2014 at 2:00 pm   *Riggs Auditorium*

Basic & Translational Science

Exploring CRISPR's potential in gene therapy:
   repair of deafness-causing Vlgr1 mutation ....Dougherty (Shin)

Red wine extract activation of basophils in vitro: evidence for etiology
   of symptom exacerbation in aspirin exacerbated respiratory disease? ....Peters (Payne)

Development of a prospective clinical trial for advanced head and neck cancer
   IGF1R expression in oral cavity squamous cell carcinoma ....McGarey (Jameson)

Preoperative Factors

Vitamin D and post-thyroidectomy hypocalcemia.. Danan (Shonka)

Correlation between dog bite severity and dog breed .... Teng (Christophel)

3D printed skull base model as a tool for rhinological surgical simulation .... Reed (Gurrola)

Expiratory disproportional index and total peak flow rate as predictors
   of stenosis severity in idiopathic subglottic stenosis .... Bakos (Daniero)

Revision nasal valve reconstruction: what failed the first time? ....Allak (Park)

Voice outcomes in surgical treatment of Zenker's diverticula..Schoeff (Daniero)

Intraoperative Techniques & Postoperative Outcomes

Does free flap ischemia time impact operative outcomes? .... Langford (Fedder/Jameson)

Advancing transoral type 1 laryngeal cleft repair:
   the trapezoidal post-cricoid mucosal advancement flap .... Miller (Early)

Supraclavicular artery island flap vs radial forearm free flap:
   a comparison of perioperative outcomes .... Koors (Fedder)

RESIDENT RESEARCH ABSTRACTS

Exploring CRISPR's potential in gene therapy: repair of deafness-causing Vlgr1 mutation

William Dougherty MD; <u>Jung-Bum Shin PhD</u>; Tingting Du PhD

<u>Objective:</u> The goal of this project is to repair deafness-causing mutations in the mouse, using the Clustered Regularly Interspaced Palindromic Repeat (CRISPR)/Cas-mediated genome editing technology, which allows targeted genetic modification of virtually any locus of interest.

<u>Design, Subjects, and Interventions:</u> In this project, we target a deafness causing mutation in the VLGR1 gene. Mutations in VLGR1, (very large g-protein receptor), are known to cause profound deafness. The overall strategy of this project is to repair the mutation in vivo, by delivering CRISPR/Cas components to inner ear hair cells using an adeno-associated virus (AAV) vector system. The first objective is to demonstrate expression of the CRISPR/Cas components in the hair cells, and the second to demonstrate repair of the targeted gene locus and restoration of hearing. Success of the project will be assessed by monitoring the expression of CRISPR/Cas components and the repair of the gene locus in vitro and in vivo, as well as restoration of protein expression, hair cell morphology, and hearing function.

<u>Results:</u> In the initial stages of the project we demonstrate the feasibility of a novel technique and study design. Specifically, demonstrating CRISPR/Cas 9 expression in wild type mice pups after AAV injection into the inner ear in the first few days of life. The procedure in wild type mice does not appear to cause inner ear trauma sufficient to result in a permanent hearing loss. Additionally, genotyping of in vitro explant cochlea also demonstrate gene editing at the targeted sequence.

<u>Conclusions:</u> Delivery of CRISPR/Cas components to the mouse inner ear via a viral vector is a feasible approach for repair of genetic hearing loss. Future efforts for this project will explore additional mutations for inner ear proteins, as hearing restoration with this approach likely depends on the critical period during which a protein is necessary for appropriate morphologic organization and creation of a functional mechanotransduction system in the hair cell.

Red wine extract activation of basophils in-vitro: evidence for etiology of symptom exacerbation in aspirin exacerbated respiratory disease?

Daniel Peters MD; Julie Negri MS; John Steinke PhD; Larry Borish MD; <u>Spencer Payne MD</u>

<u>Objective:</u> To explore the mechanisms of symptomatic exacerbation of patients with AERD on exposure to red wine

<u>Design:</u> In-vitro analysis of granulocyte activation

<u>Subjects:</u> Whole blood samples were obtained from patients without asthma (n=3), patients with asthma (n=3), and patients with aspirin sensitive asthma (n=1).

<u>Intervention:</u> Whole blood isolates and purified granulocyte populations were obtained from patients with asthma and healthy controls. These were exposed to components of red wine including ethanol, red wine extract and a representative polyphenolic compound, resveratrol. Markers of granulocyte activation were then measured via flow cytometry and ELISA for basophils and eosinophils respectively. Additionally, culture derived mast cells were also tested via ELISA.

<u>Results:</u> Exposure to red wine extract resulted in activation of basophils in all samples. Mean basophil florescence increased from a baseline of 4.2 to 8.4 following exposure to red wine extract. This was not seen with ethanol or resveratrol, nor was activation detected in mast cells (via PGD2) or eosinophils (via EDN) with any compound.

<u>Conclusion:</u> One mechanism for symptom exacerbation with exposure to red wine appears to be through basophil activation via the non-alcoholic components of red wine. This does not appear to be secondary to resveratrol. Additional studies with other phenolic compounds will need to be performed.

Development of a prospective clinical trial for advanced head and neck cancer: IGF1R expression in oral cavity squamous cell carcinoma

Patrick McGarey MD; Matthew Hubbard MD; Lane Donaldson MD; Henry Frierson MD; Edward Stelow MD; Mark Jameson MD PhD

Objective: Elevated IGF1R expression has been correlated with worse prognosis in certain head and neck cancer cohorts and may be a predictive marker of response to EGFR antagonists. We sought to correlate IGF1R expression and survival in oral cavity squamous cell carcinoma (OCSCC).

Study Design: Tissue microarray of 200 OCSCC samples stained for IGF1R expression, retrospective chart review. IGF1R expression level was scored on a 1-4 scale based on percentage of cells stained and intensity of staining; elevated IGF1R expression was defined as a composite score ≥ 3. Overall survival (OS) was correlated with IGF1R expression level for various treatment groups.

Results: 178 samples were suitable for IGF1r expression analysis. Patients were treated with surgical excision and postoperative adjuvant therapy based on standard of care guidelines. Among the entire cohort, elevated IGF1R expression trended towards lower OS at 3 years (53.9% vs 63.0% for low IGF1R expression, n=178, p=0.053). Among patients with advanced disease (stage III/IV), high IGF1R expression correlated with lower OS at 3 years (41.5% vs 64.1% for low IGF1R expression, n=108, p=0.029). Among patients with indications for adjuvant chemoradiotherapy, IGF1R expression trended towards lower OS at 3 years (34.1% vs 64.2% for low IGF1R expression, n=47, p=0.068).

Conclusions: Tumor expression of IGF1R may have negative prognostic value for patients with OCSCC, especially in cohorts with advanced disease. Further research is needed to assess if this cohort responds favorably to treatment with EGFR antagonists.

Vitamin D and post-thyroidectomy hypocalcemia

Deepa Danan MD MBA; David Shonka MD

Background: Hypocalcemia is the most common complication after total thyroidectomy(TT). While several studies have sought to identify predictors of postoperative hypocalcemia, there have been conflicting results regarding the impact of preoperative vitamin D deficiency(VDD). This study hypothesizes that VDD correlates with temporary hypocalcemia after TT only in patients with transient parathyroid gland(PG) injury.

Methods: The medical records of patients undergoing TT were retrospectively reviewed and multiple data collected. The number of PG identified intraoperatively(PII) was used as a marker of transient parathyroid damage based on prior studies. Patients with 3 or more glands identified were classified as "high risk."

Results: A total of 67 patients were included in the study. Factors predictive of postoperative serum calcium level included the preoperative 25(OH)D level, presence of preoperative VDD, performance of CCND, and postoperative PTH level. When separating high and low risk patients, preoperative 25(OH)D level and VDD remained significant predictors of postoperative calcium levels only in high risk patients. When considering the outcome of postoperative hypocalcemia, VDD was only a significant predictor of postoperative hypocalcemia in high risk patients (OR 5.8, p=0.036).

Conclusions: Previous studies have conflicting results regarding the impact of VDD on hypocalcemia after TT. The present study demonstrates that VDD is a significant predictor of postoperative hypocalcemia in patients in whom 3 or 4 parathyroid glands are identified intraoperatively, but not in patients who sustain minimal transient damage to the parathyroid glands. In high risk patients, VDD led to a 5.8 times higher risk of postoperative hypocalcemia.

Correlation between dog bite severity and dog breed

James Teng MD; Shefali Rikhi MS3; Jared Christophel MD MPH

Objective: Dog bites cause a significant health burden in the United States. Certain breeds have a higher propensity to bite. This study seeks to examine the relationship between dog breeds and dog bite severity.

Design: Case series.

Methods: Retrospective chart review performed on all patients with dog bite injuries to the head and neck between 1/1/1998 and 6/1/2016. Demographic information was collected. Injury information, including dog breed, type of injury, injury subsite, and treatment method, was collected. Injury classification was stratified based on treatment method. Data analysis was performed using Microsoft Excel 2010.

Results: Over half of victims were female (67%). The majority of victims were <10 years of age (59%). Pitbulls (16.7%) and rottweilers (11.1%) were the two breeds most commonly cited for dog bite injuries and had consistently high bite severity. Other breeds with high bite severity were not cited as frequently for causing injuries.

Conclusion: Pitbulls and rottweilers have high bite frequencies and high bite severity. Based on this information, the risk of ownership of these breeds is higher compared to owning other breeds with high potential for severe bite but low bite frequency. Physicians who treat dog bite injuries, as well as current and prospective dog owners, should be aware of the potential risks associated with certain breeds.

3D printed skull base model as a tool for rhinological surgical simulation

Robert Reed MD; Spencer Payne MD; Jose Gurrola MD

Objective: Examine the utility of a 3D printed model of the nose, paranasal sinuses, and anterior skull base as a tool to learn basic rhinological procedures.

Design: Randomized controlled study. Subjects attended a lecture on nasal/paranasal sinus anatomy and basic rhinological procedures. Participants were then separated into a control group and active group. The control group participants performed recorded basic rhinological endoscopic procedures on a cadaver head. Active group participants practiced these procedures on our 3D printed model prior to "testing" on a cadaver head.

Subjects: OHNS interns (2), junior NSGY residents (4), allergy/immunology fellows (1), and medical students (18) interested in these fields participated in the study.

Intervention(s): The endoscopy videos were blindly graded by our two attending rhinologists based on diagnostic endoscopy technique, maintenance of endoscopic orientation, overall grade for the debridement exercise, and overall grade for the epistaxis simulation.

Results: Between the two groups, no statistically significant differences were noted in each of the four graded fields. However, an overall composite grade did reach significance (p-value = 0.006). Survey results showed statistically significantly higher scores in active group participants with higher score in confidence with endoscopy, perception of quality, and confidence with debridement.

Conclusions: Use of our 3D model did show evidence of efficacy in learning basic rhinological procedures and could be a valuable educational resource for junior otolaryngology trainees.

Expiratory disproportional index and total peak flow rate as predictors of stenosis severity in idiopathic subglottic stenosis

Stephen Bakos MD PhD; Delaney Carpenter MS4; James Daniero MD

Objective: This research project examines the utility of two pulmonary function test measures, expiratory disproportional index (EDI) and total peak flow rate (TPFR), in predicting the degree of stenosis in idiopathic subglottic stenosis.

Design & Participants: Retrospective review of data collected prospectively from adult patients presenting to UVA with idiopathic subglottic stenosis. Twenty-eight patients were included in this study. Demographics, pulmonary function test, and grade of subglottic stenosis using Cotton-Meyer classification were collected at different stages of treatment for each participant.

Results: The mean EDI for Cotton-Meyer (CM) subglottic stenosis grade I (<50% stenosis), II (51-70% stenosis), and III (71-99% stenosis) were 45.4, 58.4, and 80.0, respectively. The mean TPFR for CM grade I, II, and III were 8.9, 6.8, and 5.4, respectively. The optimal EDI value in predicting CM grade II/III stenosis was 51.1 with a specificity and sensitivity of 76.6% and 73.2%, respectively. The optimal TPFR value in predicting CM grade II/III subglottic stenosis was 7.55 with a specificity and sensitivity of 91.7% and 72.5%. There were no complications observed.

Conclusions: This study demonstrates that EDI and TPFR can be used as objective measures to predict the degree of idiopathic subglottic stenosis. These results suggest that patients with known idiopathic subglottic stenosis can be monitored as an outpatient with pulmonary function tests without direct visualization until the EDI and/or TPFR threshold are met correlating to higher grade of subglottic stenosis.

Revision nasal valve reconstruction: what failed the first time?

Amir Allak MD MBA; Jared Christophel MD MPH; Stephen Park MD

Objective: To determine the factors that require patients to undergo revision nasal valve reconstruction.

Design: Retrospective chart review, case series

Patients: Inclusion criteria included 1) History of prior nasal valve surgery 2) Subjective and objective functional/obstructive nasal airway findings 3) Those who elected to undergo revision nasal valve reconstruction. 41 patients met these criteria and 5 were excluded for history of cleft lip, sinonasal inflammatory disease, and incomplete records.

Results: Of those studied, 60% (n=21) had objective collapse of the internal valve, 29% (10) of the external valve, and 54% (19) of the inter-valve area. Previously unaddressed lower lateral cartilage anomalies (recurvature, bossae) were present in 51% (18) of cases. In those whom alar batten grafts had been previously utilized (n=6, 17%), these were found to be malpositioned 100% of the time. Operative intervention largely included autograft cartilage, the majority from the auricle (78%, n=25) and rib (13%, n=4). Revision septoplasty was performed in 63% (n=22). The most common maneuvers were revision lateral wall batten grafts (77%, n=27), dorsal onlay grafts (43%, n=15), and lower lateral cartilage modification (51%, n=18).

Conclusions: Revision nasal valve reconstruction is most commonly secondary to persistent pathology at the lateral nasal wall. Failure to identify and address lower lateral cartilage anomalies and malposition of alar batten grafts can lead to persistent postoperative obstruction.

Voice outcomes in surgical treatment of Zenker's diverticula

Stephen Schoeff MD; Michael Freeman MS4; James Daniero MD

Objective: Define the impact on voice of Zenker's diverticula and the benefit from repair.

Materials and Methods: Retrospective chart review of fifteen patients from November 2014 through April 2016 with a diagnosis of Zenkers diverticulum presenting for surgical treatment in a tertiary care center. Four patients were excluded based on incomplete records or concomitant esophageal pathology. The VHI-10 and EAT-10 were collected as part of standard clinical pre-operative and post-operative evaluation, with an average post-operative follow up of 93 days. Patients underwent treatment via one of three methods: transoral endoscopic laser diverticulotomy, or transcervical diverticulopexy or diverticulectomy. The primary outcome measure was subjective voice improvement, and secondary outcome was swallowing function improvement. Statistical analysis was performed with the Wilcoxon Signed-Ranks Test.

Results: As expected, there is a statistically significant improvement (p=0.002) in the patient reported dysphagia symptoms as measured by the EAT-10 questionnaire. However, there is also a clinically relevant and statistically significant improvement in subjective voice quality (average pre-operative total 6.55, post-operative 1.82, p=0.018) as measured by the VHI-10 questionnaire in patients undergoing surgical treatment of Zenkers diverticuli.

Conclusions: Voice is a less prominent and under-recognized complaint in patients suffering from Zenkers diverticuli, but many experience subjective voice handicap. Most note improvement in voice quality post-operatively, which we were able to quantify using the voice handicap index. We consider this a relevant consideration in pre-operative evaluation.

Does free flap ischemia time impact operative outcomes?

Brian Langford MD; Zenia Chow MBBS; Mark Jameson MD PhD; Katie Fedder MD

Objective: To investigate the impact of free flap ischemia time on flap failure, reoperation rate, intraoperative complications, postoperative complications, and length of stay.

Design: Retrospective cohort study.

Setting: Tertiary care academic medical center.

Participants: All head and neck surgery free flap reconstructions from Aug 2014 to April 2016 (n = 61).

Main Outcome Measure: Flap failure, Reoperation rate, Intraoperative complications

Results: A total of 61 free flaps in 59 patients were studied.   Mean ischemic time was 189 minutes (range: 61-330 minutes). The overall flap success rate was 98.4%. Seven patients required revision of vascular anastomosis intraoperatively. This group did have a statistically different ischemic time with binary logistic regression. The postoperative complication rate including 1 flap loss was 17/61 (28%). Mean ischemic time was not statistically longer for patients who had vs. did not have intraoperative complications (235 vs. 183 min, p=0.06), post-operative flap specific complications (213 vs. 181 min, p=0.14), or post-operative general complications (185 vs. 189 min p=0.87). There was also no correlation between ischemic time and length of hospital stay (mean 7.7 days, R=0.18, p=0.15). Prolonged ischemic time is related to bony reconstruction (p=<0.001)

Conclusion: There is no demonstrable relationship between free flap loss and ischemic time up to 5.5 hours in head and neck reconstruction. Prolonged ischemic time is permissible for complex and complete flap inset prior to revascularization. Thus, prolonged ischemic time should not be a source of concern during head and neck reconstructive surgery.

Advancing transoral type 1 laryngeal cleft repair: the trapezoidal post-cricoid mucosal advancement flap

Matthew Miller MD; Renee Booth MS4; Stephen Early MD

Objective: We present a previously unreported surgical technique for type 1 laryngeal cleft repair and report the outcomes in a series of 22 children, ages 1 month to 56 months.

Study Design: After IRB exemption was obtained, we performed a retrospective chart review of patients who underwent type 1 laryngeal cleft repair by a single surgeon between June 2012 and April 2016.

Methods: From June 2012 to April 2016, 22 patients diagnosed with type 1 laryngeal cleft underwent surgical repair using suspension microlaryngoscopy. The most common presenting symptom was respiratory distress with feeding and all patients had failed medical management. Our surgical technique recruits redundant post-cricoid mucosa to create an inferiorly-based trapezoidal flap which is advanced superiorly and approximated to the posterior arytenoid mucosa using a single 4-0 Vicryl simple suture bilaterally. Anterior re-approximation of the arytenoid mucosa is also achieved using a single 4-0 Vicryl suture. This advancement flap repair elevates the interarytenoid notch and forms a solid posterior laryngeal wall.

Results: Average follow-up as of May 1st 2016 is 2 years and 2 months. Of the twenty-two patients in our series, all but three had significant improvement in symptoms after surgery. 14/22 (64%) patients had resolution of symptoms and 5/22 (23%) had significant improvement. 17 patients were able to tolerate a soft diet on POD 1 and were discharged home the day after surgery. All but three patients increased on the BMI growth curve at their post-operative visits.

Conclusion: The post-cricoid mucosal trapezoidal advancement flap is an effective and efficient surgical repair for type 1 laryngeal clefts. To our knowledge this is the first report to describe this method of endoscopic type 1 laryngeal cleft repair.

Supraclavicular artery island flap vs radial forearm free flap: a comparison of perioperative outcomes

Paul Koors MD; Mark Jameson MD PhD; Katie Fedder MD

Objective: To determine whether the supraclavicular artery island flap (SCAIF) is superior to the radial forearm free flap (RFFF) in terms of complications, OR time, length of hospital stay and health care costs.

Design: Retrospective case review.

Setting: Tertiary care center.

Patients: All patients who underwent SCAIF or RFFF reconstruction after oncologic resection from October 2014 to the present were included in the study.

Main Outcome Measures: The length of hospital stay, procedure time, total OR time and non-operative OR time were collected and compared between groups using T test. The flap take-back rate, failure rate and donor site complication rates were collected and compared between groups using Chi square test.

Results: Average length of hospital stay was shorter for SCAIF (6.3 days vs 5.6 days) although this was not statistically different (p=0.258). Procedure time was slightly shorter for RFFF (541 min vs 532 min) although this was not statistically significant (p=0.791). Total OR time and non-operative time were both shorter for SCAIF although neither was statistically significant (p=0.837 and p=0.232, respectively). The percentage of flap take-backs and donor site complications was lower for SCAIF although neither was statistically significant (p=0.468 and p=0.353, respectively). The flap failure rate was lower for RFFF although this was also not statistically significant (p=0.121).

Conclusion: For the group studied, the length of stay, total OR time, non-operative time, take-back rate and donor site complication rate were lower for SCAIF although none of these reached statistical significance.