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Abstract 23: Ultrasound-mediated on-demand release from ionically cross-linked hydrogel: New approach for targeted Immunotherapy in Vascularized Composite Allotransplantation

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Citation	Feturi, F. G., H. Wang, Y. Brudno, V. Erbas, L. Dong, H. Sahin, Z. Zhang, et al. 2017. "Abstract 23: Ultrasound-mediated on-demand release from ionically cross-linked hydrogel: New approach for targeted Immunotherapy in Vascularized Composite Allotransplantation." <i>Plastic and Reconstructive Surgery Global Open</i> 5 (4 Suppl): 18-19. doi:10.1097/01.GOX.0000516544.50254.a1. http://dx.doi.org/10.1097/01.GOX.0000516544.50254.a1 .
Published Version	doi:10.1097/01.GOX.0000516544.50254.a1
Citable link	http://nrs.harvard.edu/urn-3:HUL.InstRepos:33029990
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CONCLUSION: The CRISPR/Cas9 method targeted to a highly conserved sequence of *fgfr1a* introduced a diverse array of mutagenized alleles providing the opportunity to investigate suture development in correlation with new pathologic alleles. These mutations are heritable and despite the high sequence homology among genes encoding Fgf receptors, no off-target mutations have been identified to date. Initial characterization of identified alleles will focus on embryonic stages to assess the effect of mutation on Fgf signaling target genes. This analysis will be complemented by histology of zebrafish head to assess the cranial suture development and maintenance of juvenile and adult animals.

22

An Analysis of Bleeding Complications in Plastic Surgery

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PURPOSE: Our aim was to identify patient characteristics and procedures associated with bleeding complications during plastic surgery.

METHODS: The American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database was queried to identify all primary plastic surgery procedures from 2008 to 2013. Patients with bleeding complications as defined by NSQIP were identified. Patients who had a documented bleeding disorder were separately identified. Procedure CPT Codes, patient characteristics, and surgical outcomes were abstracted and analyzed to determine those procedures and conditions associated with bleeding complications. An analysis of co-morbidities, peri-operative characteristics, and post-operative complications between bleeding and non-bleeding cohorts was performed using a non-paired, 2-tailed t-test and a chi-squared test with Yates correction.

RESULTS: Of 59,184 cases identified, 1261 (2.1%) experienced bleeding complications. Regarding co-morbid conditions, 18.2% of patients had diabetes, 41.8% had hypertension, and 6.7% had bleeding disorders in the bleeding group compared with 7.4%, 25.9%, and 1.5%

in the group without bleeding complications ($p < 0.0001$). The most common primary procedures associated with bleeding complications were breast reconstruction with a free flap (20.7%) and myocutaneous trunk flaps (13.1%). The most common concurrent procedures associated with bleeding complications were breast oncology procedures (35.3%) and enterolysis (1.9%). The most common non-bleeding complication was difficulty weaning the patient off the ventilator. Twenty-five patients (2.0%) with bleeding complications died within 30 days of the procedure. Of the primary plastic surgery procedures identified, 953 (1.6%) patients carried a pre-existing diagnosis of bleeding disorder. The two most common primary procedures performed in this group were myocutaneous trunk flaps and reduction mammoplasty. The rate of bleeding complications in the group with a pre-existing bleeding disorder was more than four times the rate of bleeding complications for those without a bleeding disorder (8.9% vs. 2.0%, $p < 0.01$). In addition, the rate of other non-bleeding complications was significantly higher in the cohort with a bleeding condition (1.29% vs. 0.35%; $p < 0.01$). The most common non-bleeding complications in this cohort were prolonged ventilation requirement (2.9%) and septic shock (2.9%).

CONCLUSIONS: Plastic surgery procedures have an overall low rate of post-op bleeding (2.1%). Bleeding most commonly occurs with flap reconstruction, specifically breast and trunk flaps. A pre-operative diagnosis of hypertension, diabetes, or bleeding disorder was associated with increased incidence of post-operative bleeding complications. Two percent of patients undergoing plastic surgery procedures during our period of study had known pre-operative bleeding disorders. As these patients exhibit a significantly higher rate of post-operative bleeding as well as overall post-operative complications, recognition and appropriate management pre-operatively, potentially including risk stratification and a multi-disciplinary approach, may represent a realistic method for reducing complications in this cohort when undergoing plastic surgery procedures.

23

Ultrasound-mediated on-demand release from ionically cross-linked hydrogel: New approach for targeted Immunotherapy in Vascularized Composite Allotransplantation

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PURPOSE: More than 30,000 people receive organ transplants every year in the US. Vascularized composite allotransplantation (VCA) is the newest realm of solid organ transplantation. The skin component of VCA is highly antigenic and mandates high doses of systemic immunosuppressive drugs. Oral dosing of immunosuppressive drugs such as tacrolimus (TAC), rapamycin (Rapa), and mycophenolic acid (MPA) leads to fluctuating, erratic, or unpredictable blood levels risking toxicity or lack of efficacy. We propose a drug delivery platform that can not only provide sustained drug release but also on-cue triggered drug release upon ultrasound stimulation (USS) in graft tissues with stable, low blood levels, minimizing overall drug exposure and facilitating long-term VCA survival with no systemic complications.

METHOD: An injectable, re-loadable, biocompatible drug eluting hydrogel was prepared. We characterized the in vitro release kinetics of the drugs from alginate gels in absence and /or presence of USS. We evaluated feasibility and efficacy of the system in vivo in absence of USS. Brown Norway to Lewis rats received fully mismatched Brown Norway rat hind limb VCA (4/group) and a single dose of gel subcutaneously injected into the allograft. The gel was loaded with either TAC [10mg], Rapa [10mg], or TAC+Rapa [10mg] each in 1 ml. Drug levels in blood and VCA tissues were analyzed by LC-MS/MS. Flow cytometry was performed to detect expression of regulatory marker, FOXP3. In addition to allograft survival, systemic toxicity was evaluated using percent change in body weight (BW) and creatinine clearance (CrCL).

RESULTS: In vitro, TAC and Rapa exhibited a low baseline level (without fluctuation) of release from alginate gels in the absence of USS. Pulsatile USS triggered drug release, leading to increased drug levels after each pulse. Sustained drug release occurred from alginate gels in the absence of ultrasound with blood levels within the therapeutic range (5-10ng/ml). Drug concentration in allograft tissues was higher than in blood and contralateral limb ($P < 0.05$). In the first 2 weeks post gel injection, there was a $\leq 15\%$ change in BW which stabilized with time. BW gradually increased over time. No significant change in CrCL occurred post gel injection over time (> 0.05). Rats receiving Rapa developed Banff grade 3 rejection on day 21, while rats receiving TAC or TAC+Rapa showed allograft survival (> 100 days). Expression of the regulatory marker FOXP3 was observed which may indicate peripheral immunomodulation.

CONCLUSION: We successfully developed, for the first time, a smart hydrogel drug delivery system with sustained baseline and on-demand release of drugs upon USS for use in VCA. The TREAT™ system provides stable, low drug levels in the blood with preferential drug concentration in VCA tissues facilitating long-term VCA survival/outcomes with no systemic adverse effects. Further efforts are being made to use USS to optimize the on-cue drug release.

24

Two Locus Inheritance of Non-Syndromic Midline Craniosynostosis Via Rare SMAD6 and Common BMP2 Alleles

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