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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 ≤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.

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

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PURPOSE: Non-syndromic sagittal and/or metopic craniosynostosis, occurring once in every 4,000 live births, accounts for half of all craniosynostosis cases. Despite success in identifying the genes underlying rare syndromic craniosynostoses, mutations in these genes are very rarely found in their non-syndromic counterparts. We considered that the often sporadic occurrence of non-syndromic craniosynostosis might frequently be attributable to de novo mutation or incomplete penetrance of rare transmitted variants.

METHODS: To identify mutations contributing to common non-syndromic midline (sagittal and metopic) craniosynostosis, we performed exome sequencing of 132 parent-offspring trios and 59 additional probands.

RESULTS: Thirteen probands (7%) had damaging de novo or rare transmitted mutations in SMAD6, an inhibitor of BMP-induced osteoblast differentiation (p<10-20). SMAD6 mutations nonetheless showed striking incomplete penetrance (<60%). Genotypes of a common variant near BMP2 that is strongly associated with midline craniosynostosis explained nearly all the phenotypic variation in these kindreds, with highly significant evidence of genetic interaction between these loci via both association and analysis of linkage. A de novo mutation in SMURF1, a SMAD6 binding partner, was also identified.

CONCLUSION: This epistatic interaction of rare and common variants defines the most frequent cause of midline craniosynostosis and has implications for the genetic basis of other diseases.

Normative Values for the BREAST-Q

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PURPOSE: The BREAST-Q measures patient satisfaction and well-being in breast surgery patients. It is a widely used, rigorously developed, patient-reported outcome questionnaire. However, there currently are no published normative values for the BREAST-Q, limiting interpretability. Our primary aim was to generate normative values for the BREAST-Q. These normative values were then used as a reference point to interpret BREAST-Q data in breast surgery patients.

METHODS: Participants were recruited via the Army of Women, an online community of women with and without breast cancer that promotes breast cancer research. Participants completed one of the three unique pre-operative BREAST-Q questionnaires: Reduction, Augmentation, or Reconstruction. Inclusion criteria were female gender, age 18 years or greater, and no prior history of breast surgery or breast cancer. Analysis included descriptive statistics and a linear multivariate regression to determine variables associated with scale measures. A secondary analysis compared these normative values to a selected sample of published BREAST-Q data for reduction, augmentation and breast cancer patients. Breast cancer patients were divided into the following groups: mastectomy, lumpectomy, and reconstruction with autologous tissue or implants.

RESULTS: A total of 3,618 women completed pre-operative BREAST-Q questionnaires: Reduction (n=1206), Augmentation (n=1211) and Reconstruction (n=1201). Mean age was 54.1 ± 12.8 years, mean BMI 26.6 ± 6.1, and bra-cup size ≥D was present in 39% of women (n=1403). Normative values for Satisfaction with Breasts (SwB), Psychosocial Well-being (PsWb), Sexual Well-being (SWb), Physical Well-being-Chest, and Physical Well-being-Abdomen (PhWb-C, PhWb-A) varied between modules. Negative predictors were BMI ≥30 and bra size ≥D. A comparison of normative scores to published breast surgery patient data for reduction, augmentation, and breast cancer patients. Breast cancer patients were divided into the following groups: mastectomy, lumpectomy, and reconstruction with autologous tissue or implants.

SEXUAL WELL-BEING

Sexual Well-being scores were lower than the norm after mastectomy and lumpectomy. Physical Well-being-Chest scores were lower than the norm after mastectomy and lumpectomy. Physical Well-being-Chest scores were lower than the norm after autologous reconstruction and lower than the norm after mastectomy.