# Science Abstracts

## Human Reproduction

*A.M. Jukic et al.*, **Length of Human Pregnancy and Contributors to Its Natural Variation**, *Hum Reprod* 28.10 (October 2013): 2848–2855 • *Study Question*: How variable is the length of human pregnancy, and are early hormonal events related to gestational length? *Summary Answer*: Among natural conceptions where the date of conception (ovulation) is known, the variation in pregnancy length spanned 37 days, even after excluding women with complications or preterm births. *What Is Known Already*: Previous studies of length of gestation have either estimated gestational age by last menstrual period (LMP) or ultrasound (both imperfect measures) or included pregnancies conceived through assisted reproductive technology. *Study Design, Size, Duration*: The Early Pregnancy Study was a prospective cohort study (1982–85) that followed 130 singleton pregnancies from unassisted conception to birth, with detailed hormonal measurements through the conception cycle; 125 of these pregnancies were included in this analysis. *Participants/Materials, Setting, Methods*: We calculated the length of gestation beginning at conception (ovulation) in 125 naturally conceived, singleton live births. Ovulation, implantation and corpus luteum (CL) rescue pattern were identified with urinary hormone measurements. We accounted for events that artificially shorten the natural length of gestation (Cesarean delivery or labor induction, i.e. 'censoring') using Kaplan-Meier curves and proportional hazards models. We examined hormonal and other factors in relation to length of gestation. We did not have ultrasound information to compare with our gold standard measure. *Main Results and the Role of Chance*: The median time from ovulation to birth was 268 days (38 weeks, 2 days). Even after excluding six preterm births, the gestational length range was 37 days. The coefficient of variation was higher when measured by LMP (4.9%) than by ovulation (3.7%), reflecting the variability of time of ovulation. Conceptions that took longer to implant also took longer from implantation to delivery ($P = 0.02$). CL rescue pattern (reflecting ovarian response to implantation) was predictive ($P = 0.006$): pregnancies with a rapid progesterone rise were longer than those with delayed rise (a 12-day difference in the median gestational length). Mothers with longer gestations were older ($P = 0.02$), had longer pregnancies in other births ($P < 0.0001$) and were heavier at birth ($P = 0.01$). We did not see an association between the length of gestation and several factors that have been associated with gestational length in previous studies: body mass index, alcohol intake, parity or offspring sex. *Limitations, Reasons for Caution*: The sample size was small and some exposures were rare, reducing power to detect weak associations. *Wider Implications of the Findings*: Human gestational length varies considerably even when measured exactly (from ovulation). An individual woman's deliveries tend to occur at similar gestational ages. Events in the first 2 weeks after conception are predictive of subsequent pregnancy length, and may suggest pathways underlying the timing of delivery.

## Nature

*J. Jiang et al.*, **Translating Dosage Compensation to Trisomy 21**, *Nature* 500.7462 (August 15, 2013): 296–300 • Down syndrome is a common disorder with enormous medical and social costs, caused by trisomy for chromosome 21. We tested the concept that gene imbalance across an extra chromosome can be de facto corrected by manipulating a single gene, XIST (the X-inactivation gene). Using genome editing with zinc finger nucleases, we inserted a large, inducible XIST transgene into the

DYRK1A locus on chromosome 21, in Down syndrome pluripotent stem cells. The XIST non-coding RNA coats chromosome 21 and triggers stable heterochromatin modifications, chromosome-wide transcriptional silencing and DNA methylation to form a 'chromosome 21 Barr body'. This provides a model to study human chromosome inactivation and creates a system to investigate genomic expression changes and cellular pathologies of trisomy 21, free from genetic and epigenetic noise. Notably, deficits in proliferation and neural rosette formation are rapidly reversed upon silencing one chromosome 21. Successful trisomy silencing in vitro also surmounts the major first step towards potential development of 'chromosome therapy'.

*M. A. Lancaster et al.*, **Cerebral Organoids Model Human Brain Development and Microcephaly**, *Nature* 501.7467 (September 19, 2013): 373–379 • The complexity of the human brain has made it difficult to study many brain disorders in model organisms, highlighting the need for an in vitro model of human brain development. Here we have developed a human pluripotent stem cell-derived three-dimensional organoid culture system, termed cerebral organoids, that develop various discrete, although interdependent, brain regions. These include a cerebral cortex containing progenitor populations that organize and produce mature cortical neuron subtypes. Furthermore, cerebral organoids are shown to recapitulate features of human cortical development, namely characteristic progenitor zone organization with abundant outer radial glial stem cells. Finally, we use RNA interference and patient-specific induced pluripotent stem cells to model microcephaly, a disorder that has been difficult to recapitulate in mice. We demonstrate premature neuronal differentiation in patient organoids, a defect that could help to explain the disease phenotype. Together, these data show that three-dimensional organoids can recapitulate development and disease even in this most complex human tissue.

*S.A.R. Mousavi et al.*, **Glutamate Receptor-like Genes Mediate Leaf-to-Leaf Wound Signalling**, *Nature* 500.7463 (August 22, 2013): 422–426 • Wounded leaves communicate their damage status to one another through a poorly understood process of long-distance signalling. This stimulates the distal production of jasmonates, potent regulators of defence responses. Using non-invasive electrodes we mapped surface potential changes in Arabidopsis thaliana after wounding leaf eight and found that membrane depolarizations correlated with jasmonate signalling domains in undamaged leaves. Furthermore, current injection elicited jasmonoyl-isoleucine accumulation, resulting in a transcriptome enriched in RNAs encoding key jasmonate signalling regulators. From among 34 screened membrane protein mutant lines, mutations in several clade 3 genes (GLRs 3.2, 3.3 and 3.6) attenuated wound-induced surface potential changes. Jasmonate-response gene expression in leaves distal to wounds was reduced in a glr3.3 glr3.6 double mutant. This work provides a genetic basis for investigating mechanisms of long-distance wound signalling in plants and indicates that plant genes related to those important for synaptic activity in animals function in organ-to-organ wound signalling.

*X. Tian et al.*, **High-Molecular-Mass Hyaluronan Mediates the Cancer Resistance of the Naked Mole Rat**, *Nature* 500.7458 (July 18, 2013): 346–349 • The naked mole rat (Heterocephalus glaber) displays exceptional longevity, with a maximum lifespan exceeding 30 years. This is the longest reported lifespan for a rodent species and is especially striking considering the small body mass of the naked mole rat. In comparison, a similarly sized house mouse has a maximum lifespan of 4 years. In addition to their longevity, naked mole rats show an unusual resistance to cancer. Multi-year observations of large naked mole-rat colonies did not detect a single incidence of cancer. Here we identify a mechanism responsible for the naked mole rat's cancer resistance. We found that naked mole-rat fibroblasts secrete

extremely high-molecular-mass hyaluronan (HA), which is over five times larger than human or mouse HA. This high-molecular-mass HA accumulates abundantly in naked mole-rat tissues owing to the decreased activity of HA-degrading enzymes and a unique sequence of hyaluronan synthase 2 (HAS2). Furthermore, the naked mole-rat cells are more sensitive to HA signalling, as they have a higher affinity to HA compared with mouse or human cells. Perturbation of the signalling pathways sufficient for malignant transformation of mouse fibroblasts fails to transform naked mole-rat cells. However, once high-molecular-mass HA is removed by either knocking down HAS2 or overexpressing the HA-degrading enzyme, HYAL2, naked mole-rat cells become susceptible to malignant transformation and readily form tumours in mice. We speculate that naked mole rats have evolved a higher concentration of HA in the skin to provide skin elasticity needed for life in underground tunnels. This trait may have then been co-opted to provide cancer resistance and longevity to this species.

### Nature Communications

*C. Adami and A. Hintze*, **Evolutionary Instability of Zero-Determinant Strategies Demonstrates That Winning Is Not Everything**, *Nat Commun* 4.2193 (August 1, 2013) • Zero-determinant strategies are a new class of probabilistic and conditional strategies that are able to unilaterally set the expected payoff of an opponent in iterated plays of the Prisoner's Dilemma irrespective of the opponent's strategy (coercive strategies), or else to set the ratio between the player's and their opponent's expected payoff (extortionate strategies). Here we show that zero-determinant strategies are at most weakly dominant, are not evolutionarily stable, and will instead evolve into less coercive strategies. We show that zero-determinant strategies with an informational advantage over other players that allows them to recognize each other can be evolutionarily stable (and able to exploit other players). However, such an advantage is bound to be short-lived as opposing strategies evolve to counteract the recognition.

*M. A. Mikaelsson et al.*, **Placental Programming of Anxiety in Adulthood Revealed by Igf2-Null Models**, *Nat Commun* 4.2311 (August 6, 2013) • Imprinted, maternally silenced insulin-like growth factor-2 is expressed in both the foetus and placenta and has been shown to have roles in foetal and placental development in animal models. Here we compared mice engineered to be null for the placenta-specific P0 transcript (insulin-like growth factor-2-P0 KO) to mice with disruptions of all four insulin-like growth factor-2 transcripts, and therefore null for insulin-like growth factor-2 in both placenta and foetus (insulin-like growth factor-2-total KO). Both models lead to intrauterine growth restriction but dissociate between a situation where there is an imbalance between foetal demand and placental supply of nutrients (the insulin-like growth factor-2-P0 KO) and one where demand and supply is more balanced (the insulin-like growth factor-2-total KO). Increased reactivity to anxiety-provoking stimuli is manifested later in life only in those animals where there is a mismatch between placental supply and foetal demand for nutrients during gestation. Our findings further distinguish placental dysfunction from intrauterine growth restriction and reveal a role for the placenta in long-term programming of emotional behaviour.

### PNAS

*B. L. Fredrickson et al.*, **A Functional Genomic Perspective on Human Well-Being**, *Proc Natl Acad Sci* 110.33 (August 13, 2013): 13682–13689 • To identify molecular mechanisms underlying the prospective health advantages associated with psychological well-being, we analyzed leukocyte basal gene expression profiles in 80 healthy adults who were assessed for hedonic and eudaimonic well-being, as well as potentially confounded negative psychological and behavioral factors. Hedonic and eudaimonic well-being showed similar affective correlates but highly divergent transcriptome profiles. Peripheral blood mononuclear cells from people with high levels of hedonic

well-being showed up-regulated expression of a stress-related conserved transcriptional response to adversity (CTRA) involving increased expression of proinflammatory genes and decreased expression of genes involved in antibody synthesis and type I IFN response. In contrast, high levels of eudaimonic well-being were associated with CTRA down-regulation. Promoter-based bioinformatics implicated distinct patterns of transcription factor activity in structuring the observed differences in gene expression associated with eudaimonic well-being (reduced NF-κB and AP-1 signaling and increased IRF and STAT signaling). Transcript origin analysis identified monocytes, plasmacytoid dendritic cells, and B lymphocytes as primary cellular mediators of these dynamics. The finding that hedonic and eudaimonic well-being engage distinct gene regulatory programs despite their similar effects on total well-being and depressive symptoms implies that the human genome may be more sensitive to qualitative variations in well-being than are our conscious affective experiences.

*C. Opie et al.*, **Male Infanticide Leads to Social Monogamy in Primates**, *Proc Natl Acad Sci* 110.33 (August 13, 2013): 13328–13332 • Although common in birds, social monogamy, or pair-living, is rare among mammals because internal gestation and lactation in mammals makes it advantageous for males to seek additional mating opportunities. A number of hypotheses have been proposed to explain the evolution of social monogamy among mammals: as a male mate-guarding strategy, because of the benefits of biparental care, or as a defense against infanticidal males. However, comparative analyses have been unable to resolve the root causes of monogamy. Primates are unusual among mammals because monogamy has evolved independently in all of the major clades. Here we combine trait data across 230 primate species with a Bayesian likelihood framework to test for correlated evolution between monogamy and a range of traits to evaluate the competing hypotheses. We find evidence of correlated evolution between social monogamy and both female ranging patterns and biparental care, but the most compelling explanation for the appearance of monogamy is male infanticide. It is only the presence of infanticide that reliably increases the probability of a shift to social monogamy, whereas monogamy allows the secondary adoption of paternal care and is associated with a shift to discrete ranges. The origin of social monogamy in primates is best explained by long lactation periods caused by altriciality, making primate infants particularly vulnerable to infanticidal males. We show that biparental care shortens relative lactation length, thereby reducing infanticide risk and increasing reproductive rates. These phylogenetic analyses support a key role for infanticide in the social evolution of primates, and potentially, humans.

## Science

*C. D. Fiorillo*, **Two Dimensions of Value: Dopamine Neurons Represent Reward but Not Aversiveness**, *Science* 341.6145 (August 2, 2013): 546–549 • Whereas reward (appetitiveness) and aversiveness (punishment) have been distinguished as two discrete dimensions within psychology and behavior, physiological and computational models of their neural representation have treated them as opposite sides of a single continuous dimension of "value." Here, I show that although dopamine neurons of the primate ventral midbrain are activated by evidence for reward and suppressed by evidence against reward, they are insensitive to aversiveness. This indicates that reward and aversiveness are represented independently as two dimensions, even by neurons that are closely related to motor function. Because theory and experiment support the existence of opponent neural representations for value, the present results imply four types of value-sensitive neurons corresponding to reward-ON (dopamine), reward-OFF, aversive-ON, and aversive-OFF.

*P. Francalacci et al.*, **Low-Pass DNA Sequencing of 1200 Sardinians Reconstructs European Y-Chromosome Phylogeny**, *Science* 341.6145 (August 2, 2013): 565–569 • Genetic variation within the male-specific portion of the Y

chromosome (MSY) can clarify the origins of contemporary populations, but previous studies were hampered by partial genetic information. Population sequencing of 1204 Sardinian males identified 11,763 MSY single-nucleotide polymorphisms, 6751 of which have not previously been observed. We constructed a MSY phylogenetic tree containing all main haplogroups found in Europe, along with many Sardinian-specific lineage clusters within each haplogroup. The tree was calibrated with archaeological data from the initial expansion of the Sardinian population ~7700 years ago. The ages of nodes highlight different genetic strata in Sardinia and reveal the presumptive timing of coalescence with other human populations. We calculate a putative age for coalescence of ~180,000 to 200,000 years ago, which is consistent with previous mitochondrial DNA-based estimates.

*P. Hou et al.*, **Pluripotent Stem Cells Induced from Mouse Somatic Cells by Small-Molecule Compounds**, *Science* 341.6146 (August 9, 2013): 651–654 • Pluripotent stem cells can be induced from somatic cells, providing an unlimited cell resource, with potential for studying disease and use in regenerative medicine. However, genetic manipulation and technically challenging strategies such as nuclear transfer used in reprogramming limit their clinical applications. Here, we show that pluripotent stem cells can be generated from mouse somatic cells at a frequency up to 0.2 percent using a combination of seven small-molecule compounds. The chemically induced pluripotent stem cells resemble embryonic stem cells in terms of their gene expression profiles, epigenetic status, and potential for differentiation and germline transmission. By using small molecules, exogenous "master genes" are dispensable for cell fate reprogramming. This chemical reprogramming strategy has potential use in generating functional desirable cell types for clinical applications.

*D. Lukas and T. H. Clutton-Brock*, **The Evolution of Social Monogamy in Mammals**, *Science* 341.6145 (August 2, 2013): 526–530 • The evolution of social monogamy has intrigued biologists for over a century. Here, we show that the ancestral condition for all mammalian groups is of solitary individuals and that social monogamy is derived almost exclusively from this social system. The evolution of social monogamy does not appear to have been associated with a high risk of male infanticide, and paternal care is a consequence rather than a cause of social monogamy. Social monogamy has evolved in nonhuman mammals where breeding females are intolerant of each other and female density is low, suggesting that it represents a mating strategy that has developed where males are unable to defend access to multiple females.

*D. L. Mahler et al.*, **Exceptional Convergence on the Macroevolutionary Landscape in Island Lizard Radiations**, *Science* 341.6143 (July 19, 2013): 292–295 • G. G. Simpson, one of the chief architects of evolutionary biology's modern synthesis, proposed that diversification occurs on a macroevolutionary adaptive landscape, but landscape models are seldom used to study adaptive divergence in large radiations. We show that for Caribbean Anolis lizards, diversification on similar Simpsonian landscapes leads to striking convergence of entire faunas on four islands. Parallel radiations unfolding at large temporal scales shed light on the process of adaptive diversification, indicating that the adaptive landscape may give rise to predictable evolutionary patterns in nature, that adaptive peaks may be stable over macroevolutionary time, and that available geographic area influences the ability of lineages to discover new adaptive peaks.

*G. D. Poznik et al.*, **Sequencing Y Chromosomes Resolves Discrepancy in Time to Common Ancestor of Males versus Females**, *Science* 341.6145 (August 2, 2013): 562–565 • The Y chromosome and the mitochondrial genome have been used to estimate when the common patrilineal and matrilineal ancestors of humans lived. We sequenced the genomes of 69 males from nine populations, including two in which we find basal branches of the Y-chromosome tree. We identify ancient phylogenetic

structure within African haplogroups and resolve a long-standing ambiguity deep within the tree. Applying equivalent methodologies to the Y chromosome and the mitochondrial genome, we estimate the time to the most recent common ancestor (T(MRCA)) of the Y chromosome to be 120 to 156 thousand years and the mitochondrial genome T(MRCA) to be 99 to 148 thousand years. Our findings suggest that, contrary to previous claims, male lineages do not coalesce significantly more recently than female lineages.

*S. Ramirez et al.*, **Creating a False Memory in the Hippocampus**, *Science* 341.6144 (July 26, 2013): 387–391 • Memories can be unreliable. We created a false memory in mice by optogenetically manipulating memory engram-bearing cells in the hippocampus. Dentate gyrus (DG) or CA1 neurons activated by exposure to a particular context were labeled with channelrhodopsin-2. These neurons were later optically reactivated during fear conditioning in a different context. The DG experimental group showed increased freezing in the original context, in which a foot shock was never delivered. The recall of this false memory was context-specific, activated similar downstream regions engaged during natural fear memory recall, and was also capable of driving an active fear response. Our data demonstrate that it is possible to generate an internally represented and behaviorally expressed fear memory via artificial means.

*C. A. Rietveld et al.*, **GWAS of 126,559 Individuals Identifies Genetic Variants Associated with Educational Attainment**, *Science* 340.6139 (June 21, 2013): 1467–1471 • A genome-wide association study (GWAS) of educational attainment was conducted in a discovery sample of 101,069 individuals and a replication sample of 25,490. Three independent single-nucleotide polymorphisms (SNPs) are genome-wide significant (rs9320913, rs11584700, rs4851266), and all three replicate. Estimated effects sizes are small (coefficient of determination R(2) ≈ 0.02%), approximately 1 month of schooling per allele. A linear polygenic score from all measured SNPs accounts for ≈2% of the variance in both educational attainment and cognitive function. Genes in the region of the loci have previously been associated with health, cognitive, and central nervous system phenotypes, and bioinformatics analyses suggest the involvement of the anterior caudate nucleus. These findings provide promising candidate SNPs for follow-up work, and our effect size estimates can anchor power analyses in social-science genetics.

### Science Translational Medicine

*I. Das et al.*, **Hedgehog Agonist Therapy Corrects Structural and Cognitive Deficits in a Down Syndrome Mouse Model**, *Sci Transl Med* 5.201 (September 4, 2013): 201ra120 • Down syndrome (DS) is among the most frequent genetic causes of intellectual disability, and ameliorating this deficit is a major goal in support of people with trisomy 21. The Ts65Dn mouse recapitulates some major brain structural and behavioral phenotypes of DS, including reduced size and cellularity of the cerebellum and learning deficits associated with the hippocampus. We show that a single treatment of newborn mice with the Sonic hedgehog pathway agonist SAG 1.1 (SAG) results in normal cerebellar morphology in adults. Further, SAG treatment at birth rescued phenotypes associated with hippocampal deficits that occur in untreated adult Ts65Dn mice. This treatment resulted in behavioral improvements and normalized performance in the Morris water maze task for learning and memory. SAG treatment also produced physiological effects and partially rescued both N-methyl-d-aspartate (NMDA) receptor-dependent synaptic plasticity and NMDA/AMPA receptor ratio, physiological measures associated with memory. These outcomes confirm an important role for the hedgehog pathway in cerebellar development and raise the possibility for its direct influence in hippocampal function. The positive results from this approach suggest a possible direction for therapeutic intervention to improve cognitive function for this population.

### Stem Cell Reports

*M. Miyanishi et al.*, **Do Pluripotent Stem Cells Exist in Adult Mice as Very Small Embryonic Stem Cells?**, *Stem Cell Reports* 1.2 (July 24, 2013): 198–208 • Very small embryonic-like stem cells (VSELs) isolated from bone marrow (BM) have been reported to be pluripotent. Given their nonembryonic source, they could replace blastocyst-derived embryonic stem cells in research and medicine. However, their multiple-germ-layer potential has been incompletely studied. Here, we show that we cannot find VSELs in mouse BM with any of the reported stem cell potentials, specifically for hematopoiesis. We found that: (1) most events within the "VSEL" flow-cytometry gate had little DNA and the cells corresponding to these events (2) could not form spheres, (3) did not express Oct4, and (4) could not differentiate into blood cells. These results provide a failure to confirm the existence of pluripotent VSELs.