Science Abstracts

Cell

M. Ginsberg et al., **Efficient Direct Reprogramming of Mature Amniotic Cells into Endothelial Cells by ETS Factors and TGF · Suppression**, *Cell* 151.3 (October 26, 2012): 559–575 · ETS transcription factors *ETV2*, *FLI1*, and *ERG1* specify pluripotent stem cells into induced vascular endothelial cells (iVECs). However, iVECs are unstable and drift toward nonvascular cells. We show that human midgestation c-Kit(-) lineage-committed amniotic cells (ACs) can be reprogrammed into vascular endothelial cells (rAC-VECs) without transitioning through a pluripotent state. Transient *ETV2* expression in ACs generates immature rAC-VECs, whereas coexpression with *FLI1/ERG1* endows rAC-VECs with a vascular repertoire and morphology matching mature endothelial cells (ECs). Brief TGFβ-inhibition functionalizes VEGFR2 signaling, augmenting specification of ACs into rAC-VECs. Genome-wide transcriptional analyses showed that rAC-VECs are similar to adult ECs in which vascular-specific genes are expressed and nonvascular genes are silenced. Functionally, rAC-VECs form stable vasculature in Matrigel plugs and regenerating livers. Therefore, short-term *ETV2* expression and TGFβ inhibition with constitutive *ERG1/FLI1* coexpression reprogram mature ACs into durable rAC-VECs with clinical-scale expansion potential. Banking of HLA-typed rAC-VECs establishes a vascular inventory for treatment of diverse disorders.

J. Jia et al., **Regulation of Pluripotency and Self-Renewal of ESCs through Epigenetic-Threshold Modulation and mRNA Pruning**, *Cell* 151.3 (October 26, 2012): 576–589 · Embryonic stem cell (ESC) pluripotency requires bivalent epigenetic modifications of key developmental genes regulated by various transcription factors and chromatin-modifying enzymes. How these factors coordinate with one another to maintain the bivalent chromatin state so that ESCs can undergo rapid self-renewal while retaining pluripotency is poorly understood. We report that Utf1, a target of Oct4 and Sox2, is a bivalent chromatin component that buffers poised states of bivalent genes. By limiting PRC2 loading and histone 3 lysine-27 trimethylation, Utf1 sets proper activation thresholds for bivalent genes. It also promotes nuclear tagging of messenger RNAs (mRNAs) transcribed from insufficiently silenced bivalent genes for cytoplasmic degradation through mRNA decapping. These opposing functions of Utf1 promote coordinated differentiation. The mRNA degradation function also ensures rapid cell proliferation by blocking the Myc-Arf feedback control. Thus, Utf1 couples the core pluripotency factors with Myc and PRC2 networks to promote the pluripotency and proliferation of ESCs.

J. Lee et al., **Activation of Innate Immunity Is Required for Efficient Nuclear Reprogramming**, *Cell* 151.3 (October 26, 2012): 547–558 · Retroviral overexpression of reprogramming factors (Oct4, Sox2, Klf4, c-Myc) generates induced pluripotent stem cells (iPSCs). However, the integration of foreign DNA could induce genomic dysregulation. Cell-permeant proteins (CPPs) could overcome this limitation. To date, this approach has proved exceedingly inefficient. We discovered a striking difference in the pattern of gene expression induced by viral versus CPP-based delivery of the reprogramming factors, suggesting that a signaling pathway required for efficient nuclear reprogramming was activated by the retroviral, but not CPP approach. In gain- and loss-of-function studies, we find

that the toll-like receptor 3 (TLR3) pathway enables efficient induction of pluripotency by viral or mmRNA approaches. Stimulation of TLR3 causes rapid and global changes in the expression of epigenetic modifiers to enhance chromatin remodeling and nuclear reprogramming. Activation of inflammatory pathways are required for efficient nuclear reprogramming in the induction of pluripotency.

J.M. Polo et al., **A Molecular Roadmap of Reprogramming Somatic Cells into iPS Cells**, *Cell* 151.7 (December 21, 2012): 1617–1632 · Factor-induced reprogramming of somatic cells into induced pluripotent stem cells (iPSCs) is inefficient, complicating mechanistic studies. Here, we examined defined intermediate cell populations poised to becoming iPSCs by genome-wide analyses. We show that induced pluripotency elicits two transcriptional waves, which are driven by c-Myc/Klf4 (first wave) and Oct4/Sox2/Klf4 (second wave). Cells that become refractory to reprogramming activate the first but fail to initiate the second transcriptional wave and can be rescued by elevated expression of all four factors. The establishment of bivalent domains occurs gradually after the first wave, whereas changes in DNA methylation take place after the second wave when cells acquire stable pluripotency. This integrative analysis allowed us to identify genes that act as roadblocks during reprogramming and surface markers that further enrich for cells prone to forming iPSCs. Collectively, our data offer new mechanistic insights into the nature and sequence of molecular events inherent to cellular reprogramming.

A. Soufi et al., **Facilitators and Impediments of the Pluripotency Reprogramming Factors' Initial Engagement with the Genome**, *Cell* 151.5 (November 21, 2012): 999–1004 · The ectopic expression of transcription factors can reprogram cell fate, yet it is unknown how the initial binding of factors to the genome relates functionally to the binding seen in the minority of cells that become reprogrammed. We report a map of Oct4, Sox2, Klf4, and c-Myc (O, S, K, and M) on the human genome during the first 48 hr of reprogramming fibroblasts to pluripotency. Three striking aspects of the initial chromatin binding events include an unexpected role for c-Myc in facilitating OSK chromatin engagement, the primacy of O, S, and K as pioneer factors at enhancers of genes that promote reprogramming, and megabase-scale chromatin domains spanned by H3K9me3, including many genes required for pluripotency, that prevent initial OSKM binding and impede the efficiency of reprogramming. We find diverse aspects of initial factor binding that must be overcome in the minority of cells that become reprogrammed.

Cell Stem Cell

M.C. An et al., **Genetic Correction of Huntington's Disease Phenotypes in Induced Pluripotent Stem Cells**, *Cell Stem Cell* 11.2 (August 3, 2012): 253–263 · Huntington's disease (HD) is caused by a CAG expansion in the huntingtin gene. Expansion of the polyglutamine tract in the huntingtin protein results in massive cell death in the striatum of HD patients. We report that human induced pluripotent stem cells (iPSCs) derived from HD patient fibroblasts can be corrected by the replacement of the expanded CAG repeat with a normal repeat using homologous recombination, and that the correction persists in iPSC differentiation into DARPP-32-positive neurons in vitro and in vivo. Further, correction of the HD-iPSCs normalized pathogenic HD signaling pathways (cadherin, TGF-β, BDNF, and caspase activation) and reversed disease phenotypes such as susceptibility to cell death and altered mitochondrial bioenergetics in neural stem cells. The ability to make patient-specific, genetically corrected iPSCs from HD patients will provide relevant disease models in identical genetic backgrounds and is a critical step for the eventual use of these cells in cell replacement therapy.

Y. Buganim et al., **Direct Reprogramming of Fibroblasts into Embryonic Sertoli-like Cells by Defined Factors**, *Cell Stem Cell* 11.3 (September 7, 2012): 373–386 · Sertoli cells are considered the "supporting cells"

of the testis that play an essential role in sex determination during embryogenesis and in spermatogenesis during adulthood. Their essential roles in male fertility along with their immunosuppressive and neurotrophic properties make them an attractive cell type for therapeutic applications. Here we demonstrate the generation of induced embryonic Sertoli-like cells (ieSCs) by ectopic expression of five transcription factors. We characterize the role of specific transcription factor combinations in the transition from fibroblasts to ieSCs and identify key steps in the process. Initially, transduced fibroblasts underwent a mesenchymal to epithelial transition and then acquired the ability to aggregate, formed tubular-like structures, and expressed embryonic Sertoli-specific markers. These Sertoli-like cells facilitated neuronal differentiation and self-renewal of neural progenitor cells (NPCs), supported the survival of germ cells in culture, and cooperated with endogenous embryonic Sertoli and primordial germ cells in the generation of testicular cords in the fetal gonad.

B.P. Hermann et al., **Spermatogonial Stem Cell Transplantation into Rhesus Testes Regenerates Spermatogenesis Producing Functional Sperm**, *Cell Stem Cell* 11.5 (November 2, 2012): 715–726 · Spermatogonial stem cells (SSCs) maintain spermatogenesis throughout a man's life and may have application for treating some cases of male infertility, including those caused by chemotherapy before puberty. We performed autologous and allogeneic SSC transplantations into the testes of 18 adult and 5 prepubertal recipient macaques that were rendered infertile with alkylating chemotherapy. After autologous transplant, the donor genotype from lentivirus-marked SSCs was evident in the ejaculated sperm of 9/12 adult and 3/5 prepubertal recipients after they reached maturity. Allogeneic transplant led to donor-recipient chimerism in sperm from 2/6 adult recipients. Ejaculated sperm from one recipient transplanted with allogeneic donor SSCs were injected into 85 rhesus oocytes via intracytoplasmic sperm injection. Eighty-one oocytes were fertilized, producing embryos ranging from four-cell to blastocyst with donor paternal origin confirmed in 7/81 embryos. This demonstration of functional donor spermatogenesis following SSC transplantation in primates is an important milestone for informed clinical translation.

M. Kanatsu-Shinohara et al., **Reconstitution of Mouse Spermatogonial Stem Cell Niches in Culture**, *Cell Stem Cell* 11.4 (October 5, 2012): 567–578 · Spermatogonial stem cells (SSCs) reside in specific niches within seminiferous tubules. These niches are thought to secrete chemotactic factors for SSCs, because SSCs migrate to them upon transplantation. However, the identity of these chemotactic molecules remains unknown. Here, we established a testis feeder cell culture system and used it to identify SSC chemotactic factors. When seeded on testis cells from infertile mice, SSCs migrated beneath the Sertoli cells and formed colonies with a cobblestone appearance that were very similar to those produced by hematopoietic stem cells. Cultured cells maintained SSC activity and fertility for at least 5 months. Cobblestone colony formation depended on GDNF and CXCL12, and dominant-negative GDNF receptor transfection or CXCL12 receptor deficiency reduced SSC colonization. Moreover, GDNF upregulated CXCL12 receptor expression, and CXCL12 transfection in Sertoli cells increased homing efficiency. Overall, our findings identify GDNF and CXCL12 as SSC chemotactic factors in vitro and in vivo.

M. Karow et al., **Reprogramming of Pericyte-Derived Cells of the Adult Human Brain into Induced Neuronal Cells**, *Cell Stem Cell* 11.4 (October 5, 2012): 471–476 · Reprogramming of somatic cells into neurons provides a new approach toward cell-based therapy of neurodegenerative diseases. A major challenge for the translation of neuronal reprogramming into therapy is whether the adult human brain contains cell populations amenable to direct somatic cell conversion. Here we show that cells from the adult human cerebral cortex expressing

pericyte hallmarks can be reprogrammed into neuronal cells by retrovirus-mediated coexpression of the transcription factors Sox2 and Mash1. These induced neuronal cells acquire the ability of repetitive action potential firing and serve as synaptic targets for other neurons, indicating their capability of integrating into neural networks. Genetic fate-mapping in mice expressing an inducible Cre recombinase under the tissue-nonspecific alkaline phosphatase promoter corroborated the pericytic origin of the reprogrammed cells. Our results raise the possibility of functional conversion of endogenous cells in the adult human brain to induced neuronal fates.

K. Kato et al., **Ethical and Policy Issues in the Clinical Translation of Stem Cells: Report of a Focus Session at the ISSCR Tenth Annual Meeting**, *Cell Stem Cell* 11.6 (December 7, 2012): 765–767 · Alongside the scientific barriers to the clinical translation of stem cell research are ethical and regulatory hurdles. Some of these challenges described by the Ethics and Public Policy Committee at the ISSCR Tenth Annual Meeting are presented here.

Nature

1000 Genomes Project Consortium, **An Integrated Map of Genetic Variation from 1,092 Human Genomes**, *Nature* 491.7422 (November 1, 2012): 56–65 · By characterizing the geographic and functional spectrum of human genetic variation, the 1000 Genomes Project aims to build a resource to help to understand the genetic contribution to disease. Here we describe the genomes of 1,092 individuals from 14 populations, constructed using a combination of low-coverage whole-genome and exome sequencing. By developing methods to integrate information across several algorithms and diverse data sources, we provide a validated haplotype map of 38 million single nucleotide polymorphisms, 1.4 million short insertions and deletions, and more than 14,000 larger deletions. We show that individuals from different populations carry different profiles of rare and common variants, and that low-frequency variants show substantial geographic differentiation, which is further increased by the action of purifying selection. We show that evolutionary conservation and coding consequence are key determinants of the strength of purifying selection, that rare-variant load varies substantially across biological pathways, and that each individual contains hundreds of rare non-coding variants at conserved sites, such as motif-disrupting changes in transcription-factor-binding sites. This resource, which captures up to 98% of accessible single nucleotide polymorphisms at a frequency of 1% in related populations, enables analysis of common and low-frequency variants in individuals from diverse, including admixed, populations.

A. Abyzov et al., **Somatic Copy Number Mosaicism in Human Skin Revealed by Induced Pluripotent Stem Cells**, *Nature* 492.7429 (December 20, 2012): 438–442 · Reprogramming somatic cells into induced pluripotent stem cells (iPSCs) has been suspected of causing *de novo* copy number variation. To explore this issue, here we perform a whole-genome and transcriptome analysis of 20 human iPSC lines derived from the primary skin fibroblasts of seven individuals using next-generation sequencing. We find that, on average, an iPSC line manifests two copy number variants (CNVs) not apparent in the fibroblasts from which the iPSC was derived. Using PCR and digital droplet PCR, we show that at least 50% of those CNVs are present as low-frequency somatic genomic variants in parental fibroblasts (that is, the fibroblasts from which each corresponding human iPSC line is derived), and are manifested in iPSC lines owing to their clonal origin. Hence, reprogramming does not necessarily lead to *de novo* CNVs in iPSCs, because most of the line-manifested CNVs reflect somatic mosaicism in the human skin. Moreover, our findings demonstrate that clonal expansion, and iPSC lines in particular, can be used as a discovery tool to reliably detect low-frequency CNVs in the tissue of origin. Overall, we estimate that approximately 30%

of the fibroblast cells have somatic CNVs in their genomes, suggesting widespread somatic mosaicism in the human body. Our study paves the way to understanding the fundamental question of the extent to which cells of the human body normally acquire structural alterations in their DNA post-zygotically.

F. Antonica et al., **Generation of Functional Thyroid from Embryonic Stem Cells**, *Nature* 491.7422 (November 1, 2012): 66–71 · The primary function of the thyroid gland is to metabolize iodide by synthesizing thyroid hormones, which are critical regulators of growth, development and metabolism in almost all tissues. So far, research on thyroid morphogenesis has been missing an efficient stem-cell model system that allows for the *in vitro* recapitulation of the molecular and morphogenic events regulating thyroid follicular-cell differentiation and subsequent assembly into functional thyroid follicles. Here we report that a transient overexpression of the transcription factors NKX2–1 and PAX8 is sufficient to direct mouse embryonic stem-cell differentiation into thyroid follicular cells that organize into three-dimensional follicular structures when treated with thyrotropin. These in vitro-derived follicles showed appreciable iodide organification activity. Importantly, when grafted in vivo into athyroid mice, these follicles rescued thyroid hormone plasma levels and promoted subsequent symptomatic recovery. Thus, mouse embryonic stem cells can be induced to differentiate into thyroid follicular cells in vitro and generate functional thyroid tissue.

V. M. Bedell et al., **In vivo Genome Editing Using a High-Efficiency TALEN System**, *Nature* 491.7422 (November 1, 2012): 114–118 · The zebrafish (*Danio rerio*) is increasingly being used to study basic vertebrate biology and human disease with a rich array of *in vivo* genetic and molecular tools. However, the inability to readily modify the genome in a targeted fashion has been a bottleneck in the field. Here we show that improvements in artificial transcription activator-like effector nucleases (TALENs) provide a powerful new approach for targeted zebrafish genome editing and functional genomic applications. Using the GoldyTALEN modified scaffold and zebrafish delivery system, we show that this enhanced TALEN toolkit has a high efficiency in inducing locus-specific DNA breaks in somatic and germline tissues. At some loci, this efficacy approaches 100%, including biallelic conversion in somatic tissues that mimics phenotypes seen using morpholino-based targeted gene knockdowns. With this updated TALEN system, we successfully used single-stranded DNA oligonucleotides to precisely modify sequences at predefined locations in the zebrafish genome through homology-directed repair, including the introduction of a custom-designed *EcoRV* site and a modified *loxP* (*mloxP*) sequence into somatic tissue *in vivo*. We further show successful germline transmission of both *EcoRV* and *mloxP* engineered chromosomes. This combined approach offers the potential to model genetic variation as well as to generate targeted conditional alleles.

Cancer Genome Atlas Network, **Comprehensive Molecular Portraits of Human Breast Tumours**, *Nature* 490.7418 (October 4, 2012): 61–70 · We analysed primary breast cancers by genomic DNA copy number arrays, DNA methylation, exome sequencing, messenger RNA arrays, microRNA sequencing and reverse-phase protein arrays. Our ability to integrate information across platforms provided key insights into previously defined gene expression subtypes and demonstrated the existence of four main breast cancer classes when combining data from five platforms, each of which shows significant molecular heterogeneity. Somatic mutations in only three genes (*TP53*, *PIK3CA* and *GATA3*) occurred at >10% incidence across all breast cancers; however, there were numerous subtype-associated and novel gene mutations including the enrichment of specific mutations in *GATA3*, *PIK3CA* and *MAP3K1* with the luminal A subtype. We identified two novel protein-expression-defined subgroups, possibly produced by stromal/microenvironmental elements, and

integrated analyses identified specific signalling pathways dominant in each molecular subtype including a HER2/phosphorylated HER2/EGFR/phosphorylated EGFR signature within the HER2-enriched expression subtype. Comparison of basal-like breast tumours with high-grade serous ovarian tumours showed many molecular commonalities, indicating a related aetiology and similar therapeutic opportunities. The biological finding of the four main breast cancer subtypes caused by different subsets of genetic and epigenetic abnormalities raises the hypothesis that much of the clinically observable plasticity and heterogeneity occurs within, and not across, these major biological subtypes of breast cancer.

W. Li et al., **Androgenetic Haploid Embryonic Stem Cells Produce Live Transgenic Mice**, *Nature* 490.7420 (October 18, 2012): 407–411 · Haploids and double haploids are important resources for studying recessive traits and have large impacts on crop breeding, but natural haploids are rare in animals. Mammalian haploids are restricted to germline cells and are occasionally found in tumours with massive chromosome loss. Recent success in establishing haploid embryonic stem (ES) cells in medaka fish and mice raised the possibility of using engineered mammalian haploid cells in genetic studies. However, the availability and functional characterization of mammalian haploid ES cells are still limited. Here we show that mouse androgenetic haploid ES (ahES) cell lines can be established by transferring sperm into an enucleated oocyte. The ahES cells maintain haploidy and stable growth over 30 passages, express pluripotent markers, possess the ability to differentiate into all three germ layers *in vitro* and *in vivo*, and contribute to germlines of chimaeras when injected into blastocysts. Although epigenetically distinct from sperm cells, the ahES cells can produce viable and fertile progenies after intracytoplasmic injection into mature oocytes. The oocyte-injection procedure can also produce viable transgenic mice from genetically engineered ahES cells. Our findings show the developmental pluripotency of androgenentic haploids and provide a new tool to quickly produce genetic models for recessive traits. They may also shed new light on assisted reproduction.

J. H. Rowe et al., **Pregnancy Imprints Regulatory Memory That Sustains Anergy to Fetal Antigen**, *Nature* 490.7418 (October 4, 2012): 102–106 · Pregnancy is an intricately orchestrated process where immune effector cells with fetal specificity are selectively silenced. This requires the sustained expansion of immune-suppressive maternal FOXP3+ regulatory T cells (T(reg) cells), because even transient partial ablation triggers fetal-specific effector T-cell activation and pregnancy loss. In turn, many idiopathic pregnancy complications proposed to originate from disrupted fetal tolerance are associated with blunted maternal T(reg) expansion. Importantly, however, the antigen specificity and cellular origin of maternal T(reg) cells that accumulate during gestation remain incompletely defined. Here we show that pregnancy selectively stimulates the accumulation of maternal FOXP3+ CD4 cells with fetal specificity using tetramer-based enrichment that allows the identification of rare endogenous T cells. Interestingly, after delivery, fetal-specific T(reg) cells persist at elevated levels, maintain tolerance to pre-existing fetal antigen, and rapidly re-accumulate during subsequent pregnancy. The accelerated expansion of T(reg) cells during secondary pregnancy was driven almost exclusively by proliferation of fetal-specific FOXP3+ cells retained from prior pregnancy, whereas induced FOXP3 expression and proliferation of pre-existing FOXP3+ cells each contribute to T(reg) expansion during primary pregnancy. Furthermore, fetal resorption in secondary compared with primary pregnancy becomes more resilient to partial maternal FOXP3+ cell ablation. Thus, pregnancy imprints FOXP3+ CD4 cells that sustain protective regulatory memory to fetal antigen. We anticipate that these findings will spark further investigation on maternal regulatory T-cell specificity that unlocks new strategies for improving pregnancy outcomes

and novel approaches for therapeutically exploiting T(reg) cell memory.

PLoS One

C. Dhejne et al., **Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden**, *PLoS ONE* 6.2 (February 22, 2011): doi: 10.1371/journal.pone .0016885 · *Context*: The treatment for transsexualism is sex reassignment, including hormonal treatment and surgery aimed at making the person's body as congruent with the opposite sex as possible. There is a dearth of long term, follow-up studies after sex reassignment. *Objective*: To estimate mortality, morbidity, and criminal rate after surgical sex reassignment of transsexual persons. *Design*: A population-based matched cohort study. *Setting*: Sweden, 1973–2003. *Participants*: All 324 sex-reassigned persons (191 male-to-females, 133 female-to-males) in Sweden, 1973–2003. Random population controls (10:1) were matched by birth year and birth sex or reassigned (final) sex, respectively. *Main Outcome Measures*: Hazard ratios (HR) with 95% confidence intervals (CI) for mortality and psychiatric morbidity were obtained with Cox regression models, which were adjusted for immigrant status and psychiatric morbidity prior to sex reassignment (adjusted HR [aHR]). *Results*: The overall mortality for sex-reassigned persons was higher during follow-up (aHR 2.8; 95% CI 1.8–4.3) than for controls of the same birth sex, particularly death from suicide (aHR 19.1; 95% CI 5.8–62.9). Sex-reassigned persons also had an increased risk for suicide attempts (aHR 4.9; 95% CI 2.9–8.5) and psychiatric inpatient care (aHR 2.8; 95% CI 2.0–3.9). Comparisons with controls matched on reassigned sex yielded similar results. Female-to-males, but not male-to-females, had a higher risk for criminal convictions than their respective birth sex controls. *Conclusions*: Persons with transsexualism, after sex reassignment, have considerably higher risks for mortality, suicidal behaviour, and psychiatric morbidity than the general population. Our findings suggest that sex reassignment, although alleviating gender dysphoria, may not suffice as treatment for transsexualism, and should inspire improved psychiatric and somatic care after sex reassignment for this patient group.

Quarterly Review of Biology

W. R. Rice et al., **Homosexuality as a Consequence of Epigenetically Canalized Sexual Development**, *Q Rev Biol* 87.4 (December 2012): 343–368 · Male and female homosexuality have substantial prevalence in humans. Pedigree and twin studies indicate that homosexuality has substantial heritability in both sexes, yet concordance between identical twins is low and molecular studies have failed to find associated DNA markers. This paradoxical pattern calls for an explanation. We use published data on fetal androgen signaling and gene regulation via nongenetic changes in DNA packaging (epigenetics) to develop a new model for homosexuality. It is well established that fetal androgen signaling strongly influences sexual development. We show that an unappreciated feature of this process is reduced androgen sensitivity in XX fetuses and enhanced sensitivity in XY fetuses, and that this difference is most feasibly caused by numerous sex-specific epigenetic modifications ("epi-marks") originating in embryonic stem cells. These epi-marks buffer XX fetuses from masculinization due to excess fetal androgen exposure and similarly buffer XY fetuses from androgen underexposure. Extant data indicates that individual epi-marks influence some but not other sexually dimorphic traits, vary in strength across individuals, and are produced during ontogeny and erased between generations. Those that escape erasure will steer development of the sexual phenotypes they influence in a gonad-discordant direction in opposite sex offspring, mosaically feminizing XY offspring and masculinizing XX offspring. Such sex-specific epi-marks are sexually antagonistic (SA-epi-marks) because they canalize sexual development in the parent that produced them, but contribute to gonad-trait discordances in opposite-sex offspring when unerased. In this model, homosexuality occurs when stronger-than-average

SA-epi-marks (influencing sexual preference) from an opposite-sex parent escape erasure and are then paired with a weaker-than-average de novo sex-specific epi-marks produced in opposite-sex offspring. Our model predicts that homosexuality is part of a wider phenomenon in which recently evolved androgen-influenced traits commonly display gonad-trait discordances at substantial frequency, and that the molecular feature underlying most homosexuality is not DNA polymorphism(s), but epi-marks that evolved to canalize sexual dimorphic development that sometimes carryover across generations and contribute to gonad-trait discordances in opposite-sex descendants.

Science

V. Calcagno et al., **Flows of Research Manuscripts among Scientific Journals Reveal Hidden Submission Patterns**, *Science* 338.6110 (November 23, 2012): 1065–1069 · The study of science-making is a growing discipline that builds largely on online publication and citation databases, while prepublication processes remain hidden. Here, we report on results from a large-scale survey of the submission process, covering 923 scientific journals from the biological sciences in years 2006 to 2008. Manuscript flows among journals revealed a modular submission network, with high-impact journals preferentially attracting submissions. However, about 75% of published articles were submitted first to the journal that would publish them, and high-impact journals published proportionally more articles that had been resubmitted from another journal. Submission history affected post-publication impact: Resubmissions from other journals received significantly more citations than first-intent submissions, and resubmissions between different journal communities received significantly fewer citations.

K. Hayashi et al., **Offspring from Oocytes Derived from In Vitro Primordial Germ Cell-like Cells in Mice**, *Science* 338.6109 (November 16, 2012): 971–975 · Reconstitution of female germ cell development in vitro is a key challenge in reproductive biology and medicine. We show here that female (XX) embryonic stem cells and induced pluripotent stem cells in mice are induced into primordial germ cell-like cells (PGCLCs), which, when aggregated with female gonadal somatic cells as reconstituted ovaries, undergo X-reactivation, imprint erasure, and cyst formation, and exhibit meiotic potential. Upon transplantation under mouse ovarian bursa, PGCLCs in the reconstituted ovaries mature into germinal vesicle-stage oocytes, which then contribute to fertile offspring after in vitro maturation and fertilization. Our culture system serves as a robust foundation for the investigation of key properties of female germ cells, including the acquisition of totipotency, and for the reconstitution of whole female germ cell development in vitro.

S. Lu et al., **Probing Meiotic Recombination and Aneuploidy of Single Sperm Cells by Whole-Genome Sequencing**, *Science* 338.6114 (December 21, 2012): 1627–1630 · Meiotic recombination creates genetic diversity and ensures segregation of homologous chromosomes. Previous population analyses yielded results averaged among individuals and effected by evolutionary pressures. We sequenced 99 sperm from an Asian male by using the newly developed amplification method—multiple annealing and looping-based amplification cycles—to phase the personal genome and map recombination events at high resolution, which are nonuniformly distributed across the genome in the absence of selection pressure. The paucity of recombination near transcription start sites observed in individual sperm indicates that such a phenomenon is intrinsic to the molecular mechanism of meiosis. Interestingly, a decreased crossover frequency combined with an increase of autosomal aneuploidy is observable on a global per-sperm basis.

M. Meyer et al., **A High-Coverage Genome Sequence from an Archaic Denisovan Individual**, *Science* 338.6104 (October 12, 2012): 222–226 · We present a DNA library preparation method that has allowed us to reconstruct a high-coverage (30×) genome

sequence of a Denisovan, an extinct relative of Neandertals. The quality of this genome allows a direct estimation of Denisovan heterozygosity indicating that genetic diversity in these archaic hominins was extremely low. It also allows tentative dating of the specimen on the basis of "missing evolution" in its genome, detailed measurements of Denisovan and Neandertal admixture into present-day human populations, and the generation of a near-complete catalog of genetic changes that swept to high frequency in modern humans since their divergence from Denisovans.

A.K. Shah et al., **Some Consequences of Having Too Little**, *Science* 338.6107 (November 2, 2012): 682–685 · Poor individuals often engage in behaviors, such as excessive borrowing, that reinforce the conditions of poverty. Some explanations for these behaviors focus on personality traits of the poor. Others emphasize environmental factors such as housing or financial access. We instead consider how certain behaviors stem simply from having less. We suggest that scarcity changes how people allocate attention: It leads them to engage more deeply in some problems while neglecting others. Across several experiments, we show that scarcity leads to attentional shifts that can help to explain behaviors such as overborrowing. We discuss how this mechanism might also explain other puzzles of poverty.

G.E. Wimmer and D. Shohamy, **Preference by Association: How Memory Mechanisms in the Hippocampus Bias Decisions**, *Science* 338.6104 (October 12, 2012): 270–273 · Every day people make new choices between alternatives that they have never directly experienced. Yet, such decisions are often made rapidly and confidently. Here, we show that the hippocampus, traditionally known for its role in building long-term declarative memories, enables the spread of value across memories, thereby guiding decisions between new choice options. Using functional brain imaging in humans, we discovered that giving people monetary rewards led to activation of a preestablished network of memories, spreading the positive value of reward to nonrewarded items stored in memory. Later, people were biased to choose these nonrewarded items. This decision bias was predicted by activity in the hippocampus, reactivation of associated memories, and connectivity between memory and reward regions in the brain. These findings explain how choices among new alternatives emerge automatically from the associative mechanisms by which the brain builds memories. Further, our findings demonstrate a previously unknown role for the hippocampus in value-based decisions.

C. Zong et al., **Genome-Wide Detection of Single-Nucleotide and Copy-Number Variations of a Single Human Cell**, *Science* 338.6114 (December 21, 2012): 1622–1626 · Kindred cells can have different genomes because of dynamic changes in DNA. Single-cell sequencing is needed to characterize these genomic differences but has been hindered by whole-genome amplification bias, resulting in low genome coverage. Here, we report on a new amplification method—multiple annealing and looping-based amplification cycles (MALBAC)—that offers high uniformity across the genome. Sequencing MALBAC-amplified DNA achieves 93% genome coverage ≥1x for a single human cell at 25x mean sequencing depth. We detected digitized copy-number variations (CNVs) of a single cancer cell. By sequencing three kindred cells, we were able to identify individual single-nucleotide variations (SNVs), with no false positives detected. We directly measured the genome-wide mutation rate of a cancer cell line and found that purine-pyrimidine exchanges occurred unusually frequently among the newly acquired SNVs.