Centriole construction, now revealed by crystallography, proteomics, and imaging to be a sophisticated assembly of interlocking bricks, resembles LEGO®—albeit centrioles have remarkable dynamic capabilities, including self-assembly and dis-assembly, kinases and post-translational modifications, self-replication, and still mysterious mechanisms for transmission through each cell cycle and via the gametes during development. Centrioles are created by core proteins that aggregate to form unique ninefold-symmetrical para-crystalline cylinders. The centrosome then coalesces as a cloud of pericentriolar material (PCM) around the centriole. Together they comprise the cell’s microtubule organizing center (MTOC), which governs the shape, functions, and dynamics of the cell’s microtubule (MT) arrays. This includes the meiotic and mitotic spindle apparatus for chromosome segregation, the accuracy of which is crucial for avoiding aneuploidies and resulting cancer, birth defects, or infertility. Centrioles’ replication and transmission mechanisms—and reduplication blocks—across cell cycles and generations, are only now becoming tractable to molecular analysis, which allows research to address questions about spindle assembly with neither centrioles nor centrosomes or de novo centriole formation. Here we discuss the latest insights into centriole and centrosome assembly and function and their transgenerational inheritance.

The term “centrosome,” like “chromosome,” was coined in the late 19th century when each was recognized as being vital for cell division, development, and differentiation. Yet, the 20th century provided unequivocal proof that DNA molecules are carriers of inheritable information and the constituents of mitochondrial persistence during cell cycles and over generations. Imaging and sequencing technology to analyze chromosomal and mitochondrial genomes yielded a huge bonanza of information for chromosome researchers and geneticists.

Not so for centrosomes and their photogenic sidekicks, the centrioles [1]. Centrioles, which help to organize the mitotic spindle poles, behave capriciously during interphase, and, worse still, the eerie appearances and spooky vanishings of centrioles, together with their bizarrely orthogonal propagation, have led scholars to describe them, appropriately, as “advertisements,” “passengers,” and even, gruesomely, as “zombies.” Now, well into the 21st century, centriole and centrosome molecular architectures are finally being determined through sophisticated complementary investigations using proteomics, genomics, bioinformatics, and proximity-dependent biotin identification together with cryo-electron tomography, super-resolution dynamic microscopy, and precision inhibition in vivo and in vitro [2]. It shows that centriole formation and propagation are intricate, molecular puzzles—a bit like LEGO pieces—with polo-like kinase 4 (PLK4) as the indispensable master builder. While devising an inspired therapeutic strategy against cancer, Wong et al [3] created the PLK4 inhibitor called “centrinone.” Because many cancers have supernumerary centrioles that cause mitotic errors and aneuploidy, centrinone effectively “cures” abnormal centrosome amplification by depleting centrioles. Remarkably, removal of the drug restored the cancer cell’s centriole amplification. These findings raise questions about the regulators and licensing factors involved in centriole biogenesis [1] and whether it might be possible to prevent or treat cancer by even more precise centriole targeting.

Centriole’s core proteins are somewhat species specific (Fig 1). In humans, it appears that PLK4 triggers centriole formation, together with SPD2/CEP192, PLK1, pericentrin, CDK5/RAP2 among others, recruiting PCM to the centriole. SAS6 and BLD10/CEP135 are important for the cart-wheel’s ninefold symmetry. SAS4/CPAP tethers and/or stabilizes centriolar microtubules with CP110 at the centriole’s distal region [2]. Other proteins build the centriole cylinder, control its height, and enable propagation of the daughter procentriole during the subsequent S-phase and disengagement of the mother–daughter centriole pair at mitosis. Significantly, the temporal coupling of centriole duplication with DNA replication in the S-phase exploits the stringent blocks to DNA replication, thereby also preventing centrioles from quadruplicating [1]. Just like chromosomes, the centrioles cannot duplicate again until they have separated after mitosis.

Microtubules are dynamic polarized polymers of α- and β-tubulin, which self-assemble to form αβ-heterodimers. Recognition of the third, rarer isoform γ-tubulin has been invaluable for understanding how centrosomal molecules shape MT arrays throughout cell cycles and development. γ-tubulin ring complex (γ-TuRC), the cell’s primary MT nucleator, is composed of polymerized γ-tubulin small complex subunits (γ-TuSC),
composed themselves of two γ-tubulin molecules and one of each accessory protein, GCP2 and GCP3. Closure of the γ-TuRC ring doubles its MT-nucleating abilities, which is crucial both for initiating assembly on γ-TuRC templates and for regulating the MT array’s shape, size, and dynamics [4]. γ-tubulin, within γ-TuRC, provides the template onto which MTs grow. The centrosome’s PCM cloud, composed of about three dozen other proteins, coalesces around the centrioles and organizes the cell’s dynamic MT arrays.

Birth defects and infertility are often caused by inaccurate chromosome segregation during female meiosis; Holubcová et al [5] demonstrated the mechanisms accounting for these errors. While seemingly illogical, neither centrosomes nor centrioles are active organizing centers in human oocytes. Using sophisticated dynamic imaging of human oocytes, they showed that meiotic spindles assemble slowly and inaccurately with MTs assembling around the meiotic chromosomes driven by Ran-GTP. Under-scoring PLK4’s role in ensuring the fidelity of chromosome segregation, common variants of PLK4 predispose human embryos to mitotic-origin aneuploidy, which is in turn associated with decreased embryonic survival to blastocyst formation [6]. Wong et al [3] also identified the previously unknown “centriole loss sensor,” a new block to cell cycle reentry sensed by p53 via a still unidentified response pathway; perhaps during fertilization, the introduction of the sperm centriole overcomes this “centriole loss sensor” block in oocytes enabling zygotes to enter the first cell cycle and begin embryogenesis.

Unlike biparental inheritance of nuclear DNA and unimaternal inheritance of mitochondria, centriole and centrosome transmission is still not understood. Neither the molecules involved, nor even precise terminologies are agreed upon. Patrimonial contributions are difficult to assess since they are complicated by de novo assembly of centrioles, for example, after parthenogenesis. Ross and Normark [7] wrote that “There is sufficient evidence to demonstrate convincingly that there is no such thing as ‘centrosome duplication’ or ‘centrosome inheritance’ despite the near-universal use of these terms.” This is certainly controversial, since paternal centrioles have been reported to “exhibit exceptional persistence in C. elegans embryos” [8], and Avidor-Reiss et al [9] insightfully present a few feasible models for centrosome inheritance. Yet,
without the DNA of nuclei, chloroplasts, and mitochondria, the exact mode of transmis-
sion remains elusive, as does defining the fate of centrioles and centrosomes with
terms including “inheritance,” “ab ovo,” “de novo,” “contribution,” and “transmission.”

Deciphering the centriole’s molecular architecture raises questions as to how this miniscule structure manages to organize the entire three-dimensional MT cytoskeleton. Insights garnered recently from cell-free centrosome assembly of the coiled-coil protein SPD-5 show that it functions as the substrate on which other centrosome proteins can bind and interact [10]. Depoly-
merized SPD-5 is not functional, providing a pathway for both centrosome and MT
assembly and disassembly.

More challenges, recently insurmount-
able, can now be addressed. If the centro-
some is an MTOC cloud organized by the centriole, are directed motors, MT-binding
proteins, chromosomes, and RAN truly suffi-
cient to organize accurate bipolar spindles
without centrioles? Might nanoscopic cart-
wheels, from which centrioles do not grow, be at the acentriolar centrosome core? Is intranuclear sequestration of key centro-
some proteins, like NuMA and some CEPs, together with reduced MT dynamics and increased MT stability—in part due to γ-TuRC ring changes—sufficient to explain MT array changes between interphase and mitosis? What happens to centrioles in the last two cell cycles, that is, the first two meiotic cell cycles which generate oocytes and sperm? How is the sperm centrosome reduced? Is the sperm centriole paternally inherited and does this overcome the newly discovered centriole loss sensor in acentriolar oocytes? And how, when, and why does the oocyte lose its centrioles? Does the egg form its centrosomes de novo, as during parthenogenesis? Do mammalian embryos need to mature over a handful of cell cycles before they are old enough to obtain their centriole licenses to drive through future cell cycles? Why are rodents unique among all mammals investigated in relying on a maternal, rather than the canonical paternal, centriole? Since centrioles are tightly constrained to duplicate once and only once in each cell cycle, how do the supernumer-
ary centrioles emerge in many cancers and can they be prevented?

The LEGO Movie’s theme that Everything is Awesome “when we stick together” should resonate with centriole
and centrosome biologists. Within the seemingly rigid confines of a dozen or so uniform building blocks, centrioles enable incredible microtubule diversity, which forms the basis for cellular architecture and motility, thereby enabling development and differentiation.

References