Co-opting Moore's law: Therapeutics, vaccines and interfacially active particles manufactured via PRINT®

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ABSTRACT

Nanoparticle properties such as size, shape, deformability, and surface chemistry all play a role in nanomedicine drug delivery. While many studies address the behavior of particle systems in a biological setting, revealing how these properties work together presents unique challenges on the nanoscale. Particle replication in non-wetting templates (PRINT®) is one molding technique that allows for fabrication of “calibration quality” micro and nanoparticles with independent control over their physical parameters. As the only technology in the world capable of independently optimizing and robustly manufacturing GMP compliant precision particles of virtually any size, shape, and composition, the PRINT technology has the capability to engineer the future of healthcare.

Polymers are at the “Core” of all we do. When my group began reporting on the synthesis of novel, functionalized, photo-curable perfluoropolyethers (PFPEs) in supercritical carbon dioxide in the late 1990s, we called these materials “Liquid Teflon” [1,2]. These functional PFPE materials could be photochemically crosslinked at room temperature to yield clear, flexible, organic–solvent resistant materials that could be utilized for a variety of applications including for use in high-resolution imprint lithography. By employing these novel materials and adapting manufacturing approaches from the microelectronics industry, my group invented Particle Replication in Non-wetting Templates (PRINT®), a nano-materials manufacturing process that, for the first time, enabled the scalable fabrication of large batches of highly uniform, shape-specific nano- and microparticles from almost any chemical composition (Fig. 1) [3–10]. Three important advantages of PFPEs enhance the performance of PRINT-embossed molds: i) the low surface energy of PFPEs allow using any organic liquid to selectively fill only the mold’s cavities—without wetting the land area between the cavities—eliminating the problematic interconnecting “flash layer”; ii) organic liquids that are “pre-particle” solutions do not swell fluoropolymers; and iii) Teflon-like characteristics of PFPE molds allow for the easy removal (harvesting) of the particles from mold cavities. Thus, PRINT allows for the fabrication of particles with precise control over size (50 nm to >100 μm), shape, modulus, composition (hydrogels, thermoplastic polymers, active therapeutics, proteins, nucleic acids, imaging agents), and surface chemistries (antibodies, “stealthing” agents).

As the numerous applications for PRINT began to unfold, my group expanded to integrate expertise from multiple scientific fields (e.g. chemistry, engineering, biology, immunology, pharmaceutical sciences, medicine). As my talented, diverse team optimized this technology, important advances were made in understanding the interactions of particles in a biological setting. This knowledge provided direction to develop PRINT-based chemotherapeutic nanoparticles for treating cancer [11–16], a PRINT-based microneedle delivery system for a variety of therapeutic applications [17], and a PRINT nanoparticle-based vaccine platform [18]. PRINT has not only provided valuable insight into particle parameters essential for designing successful therapeutics, but through its development has also underscored a successful way to achieve innovation in the lab. The development and evolution of PRINT brought together talented, knowledgeable, and hard-working individuals with a wide range of academic backgrounds and life experiences—and stemming from these backgrounds and experiences—unique interests, perspectives, skills, capabilities, and problem-solving approaches. It is...
my opinion that there is no more fertile ground for innovation than a diversity of experience. A successful scientific endeavor is one that attracts a diversity of experience, draws upon the breadth and depth of that experience, and cultivates those differences, acknowledging the creativity they spark.

The PRINT technology evolved into a robust and reproducible platform to rationally design precise particles with virtually any size, shape, surface functionality, mechanical modulus and chemical composition to target therapeutic safety and efficacy (Fig. 2). Depending on the therapeutic application, PRINT particles can be tailored in size from tens of nanometers to hundreds of micrometers, in a variety of particle geometries, and with high degree of monodispersity. For example, PRINT particles smaller than 100 nm (in at least one dimension) are the “top performers” for intravenous applications while 1 μm particles have been identified as optimal for inhaled administration in pulmonary applications. The ability to manufacture PRINT particles of sizes 10 nm or smaller are limited due to the capabilities of current state of the art photolithographic techniques. Advances in lithography will be needed to generate smaller feature size master templates that can then be utilized in the PRINT process. The chemical flexibility of the PRINT technology offers many potential advantages in formulating both small molecule active pharmaceutical ingredients (API) and biologic API drug delivery systems such as targeting chemistries, improved drug/cargo loading, and delivery of sensitive cargos like peptides and nucleic acid, and combination products. In each case, the goal is to engineer a particle design that offers a novel, safe and cost-effective product and offers strong new product intellectual property. As the only technology in the world capable of independently designing and manufacturing precision particles of any size, shape and chemistry, the PRINT platform has the agility required to meet the product development needs of the healthcare industry and consistency required to address increasing regulatory demands.

Liquidia Technologies, the company founded based on PRINT, has evolved the technology to be “cGMP compliant,” required for use in U.S. human clinical trials. In order to realize the potential of the PRINT technology, scale needed to be addressed. As shown in Fig. 1, the particle fabrication process consists of a series of steps: 1) coating material, 2) filling material, and 3) collecting particles. It was realized that these types of steps were readily adaptable to a roll-to-roll process. This idea translated into a custom built roll-to-roll machine for the production of PRINT particles as shown in Fig. 3. Liquidia Technologies has invested significant effort and resources in the scale up of the PRINT manufacturing platform since the early stages of the company. Specifically during 2010–2013, with support from a cost-sharing grant awarded through the National Institute for Standards and Technology (NIST), Liquidia set a goal to demonstrate a 1000-fold throughput improvement for fabrication of nanoparticles. This was accomplished by increasing the
width of particle fabrication, the speed of the process, and the efficiency of the process. These approaches were undertaken using a combination of experimental prototyping, testing and optimization in combination with extensive computational modeling of the system. Completion of this effort in January 2013 was accompanied by the successful demonstration of 1000-fold increase in nanoparticle throughput, but perhaps more importantly, the full integration of multiple processing improvements into routine use at Liquidia, resulting in a dramatic increase in manufacturing capacity. These improved capabilities have provided Liquidia with sufficient capacity to support multiple pre-clinical and clinical development efforts. This production and development line has been used for the production of vaccine nanoparticles at cGMP compliant standards in the manufacture of LIQ001, a novel, and first generation influenza vaccine candidate evaluated in human clinical trials in 2010. The initial phase I/IIa clinical trial in influenza demonstrated the cGMP compliance and safety of PRINT particles [19]. Additionally, this platform can be scaled to satisfy potential global manufacturing needs. Due to the ubiquitous nature of nanoparticles in the field of drug delivery, the PRINT technology has been utilized across not only different therapeutic areas, but also across multiple companies focusing on various diseases. Liquidia Technologies pioneered the development of the PRINT technology focused on inhalation and vaccine therapeutic areas. These advancements led to a partnership developing products in collaboration with GlaxoSmithKline [20]. In 2013, Envisia Therapeutics, an ophthalmology focused company, spun out of Liquidia Technologies. Using the PRINT technology, Envisia is rationally designing PRINT particle therapeutics that are precisely engineered to overcome the biologic, chemical or other barriers that limit existing ocular therapies [21]. In addition, in 2014 Liquidia spun out Lq3 Pharmaceuticals, which is leveraging the unique benefits of the PRINT technology to develop innovative products in oral health [22]. Our research continues to operate at the interface of polymer chemistry, nanotechnology, and medicine with the purpose of engineering better therapies, vaccines, and medical devices. The advent of “calibration quality” particles using PRINT has provided a means for investigating and understanding the interdependent role of particle size, shape, surface functionality, and matrix composition on the fate of organic nanoparticles in biological settings. We continue to pursue therapeutic applications and, subsequently, utilize the agility of PRINT to elucidate particle parameters that are crucial for enhancing intended particle biodistribution, specific cellular interactions, manipulating intracellular location of particles, and minimizing cytotoxic “bystander” effects based upon target site and route of administration. As the only technology in the world capable of independently optimizing and robustly manufacturing precision particles of virtually any size, shape, and composition, the PRINT technology has the capability to engineer the future of healthcare.

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