Cellulose Nanocrystals as Advanced "Green" Materials for Biological and Biomedical Engineering

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Abstract

Background: Cellulose is a ubiquitous, renewable and environmentally friendly biopolymer, which has high promise to fulfil the rising demand for sustainable and biocompatible materials. Particularly, the recent progress in the synthesis of highly crystalline cellulose-based nanoscale biomaterials, namely cellulose nanocrystals (CNCs), draws significant attention from many research communities, ranging from bioresource engineering, to materials science and engineering, to biological and biomedical engineering to bionanotechnology. The feasibility of harnessing CNCs' unique biophysicochemical properties has inspired their basic and applied research, offering much promise for new biomaterials with diverse advanced functionalities. **Purpose:** This review focuses on vital issues and topics on the recent advances in CNC-based biomaterials with potential, in particular, for bionanotechnology and biological and biomedical engineering. The challenges and limitations of CNC technology are discussed as well as potential strategies to overcome them, providing an essential source of information in the exploration of possible and futuristic applications of the CNC-based functional "green" nanomaterials. **Conclusion:** CNCs offer exciting possibilities for advanced "green" nanomaterials, driving innovative research and development in a wide range of fields, including biological and biomedical engineering.

Keywords: Biological engineering, Biomedical engineering, Bionanotechnology, Cellulose nanocrystal (CNC), Cellulose, Renewable bionanomaterial

Introduction

From the beginning of human civilization, cellulose has been closely associated with human activities. Beginning with food, shelter, and energy sources to modern clothing and medicine, cellulose has affected every facet of human life. Due to its abundance and fascinating properties, cellulose has been used by humans from primitive to modern civilizations. Cellulose is universally present in cell walls of all vasular plants, algae, phytoplankton, and fungi. To a lesser extent cellulose is also present in some of marine animals, such as tunicates and sea squirts, and can even be synthesized by some microscopic organisms, like bacteria (Lynd et al., 2002; Jarvis, 2003; Habibi et al., 2010; Mohammadkazemi et al., 2015). Wherever it exists, cellulose acts as a basic reinforcing and structural material, providing structure rigidity and strength. About 40-60% of the total cell mass of the plant cell wall is composed of cellulose (Duchesne and Larson, 1989). Due

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to its ubiquitous presence in plant biomass, cellulose is believed to be one of the most abundant natural organic biopolymers on the earth.

One of the most fascinating aspects of cellulose is the fact that plants synthesize it from carbon dioxide, water and sunlight, conferring a true renewable status to this natural resource. Environmental compatibility, combined with the fact that it has little or no carbon foot print, makes cellulose a key biopolymer for the manufacture of greener and sustainable industrial materials. Currently, cellulose and its derivatives are found in medicines, cosmetics, optical films, textiles coatings, food items, packaging, and laminates (Klemm et al., 2005; 2011). Furthermore, cellulose has the potential of becoming a foundational material for future products and processes due to the fact that cellulose has the capacity to offer various properties that conventional materials cannot provide. In general, cellulose has high mechanical strength, flexibility, durability, low density, sound-damping performance properties, and hierarchical 3D support structural potential (Siro and Plackett, 2010; Kalia et al., 2011; Klemm et al., 2011). Moreover, owing to the presence of reactive functional groups on the surface of cellulose, it can be chemically modified and various functionalities can be introduced for tailoring the final properties for custom-made applications. Being chiral and biocompatible, various new applications are arising in the field of immobilization of proteins and antibodies, purification and separation of enantiomeric molecules and synthesis of cellulose composites with various synthetic and biopolymers (Kim and Yun, 2006; Pandey et al., 2010). With increasing understanding of physicochemical properties, structure and functions, cellulose and its derivatives are ever more incorporated into advanced technology and materials.

Recently, highly crystalline nanoscale materials produced from cellulose, namely cellulose nanocrystals (CNCs), drew significant attention from many research communities, ranging from Bioresourse Engineering, to Materials Science and Engineering, to Bionanotechnology. CNCs are generally rod-shaped, and this silhouette imparts attractive combinations of biophysicochemical characteristics, such as biocompatibility, high tensile strength, elasticity, optical transparency and anisotropy, and adaptable surface chemistry (Lagerwall et al., 2014). Such unique CNCs' properties have warranted the development of a broad range of new functional biomaterials, transforming research in biology, chemistry, physics, medicine, and materials science and

engineering. Specifically, the low toxicity and minimal risk to the environment (i.e., low ecotoxicological risk) of CNCs drive the development of biological and biomedical applications.

In this work, recent advances in CNC-based biomaterials with potential applications in biological and biomedical engineering are reviewed. Challenges and limitations of CNC technology are discussed, while potential strategies to overcome drawbacks are reviewed. It should be noted that this review is not meant to be comprehensive. The purpose of this review is to assemble information with respect to possible and futuristic applications of CNC-based functional nanomaterials, providing strategies that fulfill their potential as advanced "green" nanomaterials.

Cellulose: Structure and Morphology

Modern understanding about the morphology and structure of cellulose dates back to its first chemical separation by a French chemist Anselme Payen (1838) from timber (Klemm et al., 2005; Payen 1838). After this chemical separation, cellulose became one of the most intriguing materials, and in 1920s its polymeric structure was elucidated through the pioneering work of Hermann Staudinger (1920). Since this pioneering work, the structure and chemical and physical properties of cellulose have been the subject of numerous studies.

Cellulose, the reinforcement or skeletal material of the plant cell wall, is a polydisperse linear polymer of poly-β-(1, 4)-D-glucose units (Figure 1). In cellulose, the six member glucose units are in ring form called pyranoses. Two pyranose units undergo a condensation reaction to form the β-(1, 4) glycosidic bond, which is defined as two pyranose units linked together through C-1 and C-4 atom linkages; this link is also named as an acetal link. In cellulose, all the bulkier functional groups other than
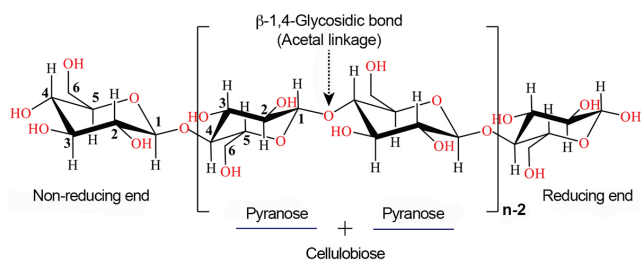

Figure 1. Basic structural unit of the cellulose chain: chemical structure and arrangements of the β-D-glucopyranose rings.

hydrogen are positioned equatorially. One end of each cellulose chain is chemically reducing in nature, displaying a hemiacetal unit, whereas the other end acts as a non-reducing part, exhibiting a hanging hydroxyl group; the reducing and non-reducing ends impart the cellulose chain with directional chemical asymmetry with respect to the two terminal ends (Habibi et al., 2010).

In the pyranose ring, during bond formation, the hydroxyl group at C-4 can interact with the carbonyl functional group at C-1 of another pyranose unit from either side of the molecule, resulting in two different spatial arrangements at C-1 position. If the hydroxyl group at C-1 is on the same side of the ring as the C-6 carbon atom, the arrangement of molecules is called a configuration and if in opposite side, it is called β configuration. In cellulose, pyranoses are in β configuration extending the molecular chain in a more or less linear direction (Smith D. H, 1937; Kalia et al., 2011). Because of this unique structural feature, cellulose displays properties such as chirality, degradability, and porosity; moreover, this biopolymer is fibrous in nature. The extensively exposed OH groups outside the ring provide extensive hydrogen bond networks, hydrophilicity, allowing for variable chemical modifications at its surface (Klemm et al., 2005; Samir et al., 2005; Kalia et al., 2011). In cellulose, both intra and intermolecular hydrogen bonding can occur. The intermolecular hydrogen bonding provides the sheet like structure, while intramolecular hydrogen bonding is mainly responsible for its stiffness and strength (Eichhorn and Davies, 2006; Zugenmaier, 2008; Nishiyama et al., 2010). The polymeric sheets of cellulose are further packed into crystals by hydrophobic interactions. The extensive hydrogen bond network strongly holds the chains together and provides cellulose with its highly ordered hierarchical 3D organization, insolubility in most organic solvents, low density, and fiber cohesiveness (Lindman et al., 2010; Lavoine, 2012; Olsson and Westman, 2013). Cellulose has several crystalline polymorphs: I, II, III, and IV. All the naturally occurring cellulose are usually of Type I and are sometimes referred to as "natural" cellulose. Cellulose Type I has two polymorphs which depend on the extent of staggering of the chains in relation to each other; I_a displays a triclinic structure, while I_β exhibits a monoclinic structure. It is important to note that triclinic and monoclinic structures coexist in different proportions, depending on the original source material (Moon et al., 2011; Chen, 2014). The I_a polymorph mostly dominates in bacteria and algae, whereas I_β polymorph

are extensively found in tunicates and higher plants (Klemm et al., 2005). Properties of cellulose fibers are also influenced by various physical, chemical and environmental factors, such as climate, maturity and harvest time, species, and methods of chemical and mechanical processing (Van de Velde and Kiekens, 2001; Kalia et al., 2011). Type I cellulose has the tendency to undergo reversible and/or irreversible conversions to other polymorphic forms when treated with different chemicals and physical protocols (Zugenmaier, 2008; Moon et al., 2011). Type II cellulose is known as regenerated cellulose. Type II cellulose is formed after re-crystallization of native cellulose with aqueous sodium hydroxide, and is most stable (Aulin et al., 2009; Lavoine et al., 2012). Type I and II cellulose also show different packing patterns. For example, Type I cellulose chains run in a parallel fashion, while Type II cellulose chains are packed in antiparallel directions with respect to each other (Khalil et al., 2012). Apart from the above mentioned cellulosic modifications, sub modifications of cellulose Type III and IV occur as III_I/ III_{II} and IV_I/ IV_{II} (Habibi et al., 2010).

The chain length of cellulose is expressed in degree of polymerization (DP). The DP value varies with the original source material and treatment methodology applied during the extraction process. DP can also be dependent on processing protocols. Cotton and other plant fibers have DP values ranging between 800-10,000, while wood pulp can display DP values between 300-1700 (Klemm et al., 2005; John and Thomas, 2008). Similar trends in DP values have been observed for cellulose produced by bacterial cells (Shi et al., 2012; Keshk, 2014).

Cellulose exists as cellulose fibers. The morphological lowest hierarchical unit of cellulose has been demarcated as elementary fibrils (Figure 2). These fibrils are arranged into larger units called microfibrils, which are in turn finally assembled into cellulose fibers (Chinga-Carrasco, 2011; Brinchi et al., 2013). One of the most interesting properties of cellulose fibrils is the presence of discontinuous crystallinity along the length. Cellulose fibrils are not fully crystalline. There are regions where cellulose chains are arranged in a highly ordered structure that results in a crystalline arrangement, which can then be flanked by a disordered chain qualified as amorphous region (Moon et al., 2011). These discontinuous crystalline regions on the cellulose fibrils are the precursors of crystalline nanocellulose (Brinchi et al., 2013).
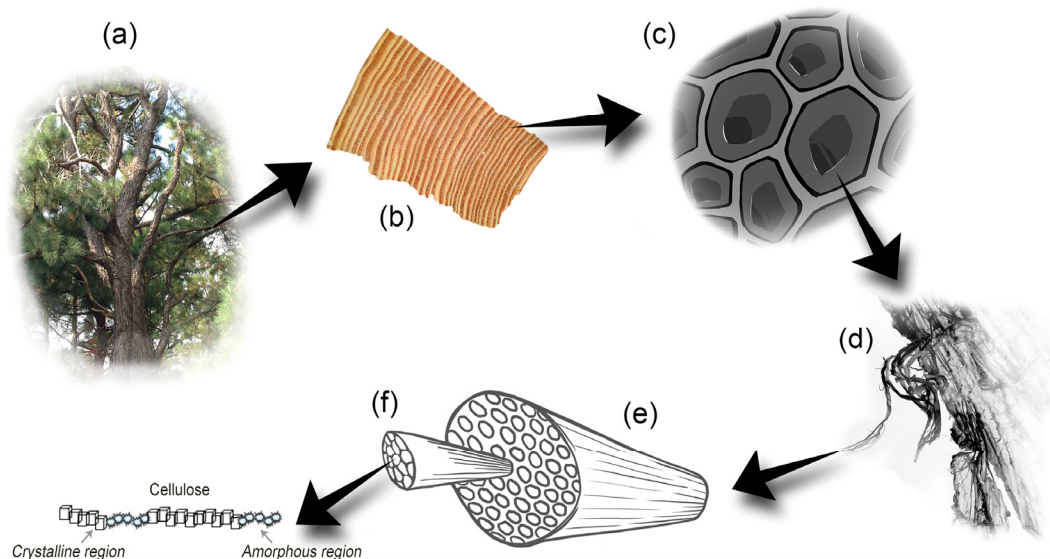
Figure 2. Structural constitution and the hierarchical arrangement of cellulose chain leading to the formation of elementary fibrils, microfibrils and the cellulose fibers: (a) biomass source of cellulose (e.g., pine tree); (b) cross-section of the pine wood; (c) cross-section of wood cellular structure, with primary and inner secondary wall thickening; (d) scanning electron microscope micrograph of milled pine wood after dilute acid (1% sulfuric acid) pretreatment, showing cellulosic fibers; (e) cellulose fiber structure; (f) cross-section, showing origin of paracrystalline arrays of microfibrils.

Cellulose Nanocrystals: Introduction

Inspired by the work of Nickerson and Habrle, Ranby reported for the first time the existence of colloidal suspensions of cellulose (Ranby, 1951; Habibi et al., 2010). Further studies on these colloidal particles through Transmission Electron Microscopy and Electron Diffraction showed needle shaped crystalline structures similar to those found on original cellulose fibers (Ranby, 1949; 1951). Further studies showed that the degradation of high quality cellulose fibers, derived from wood pulp using hydrochloric acid, followed by sonification, enabled the commercial production of microcrystalline cellulose (MCC). Since cellulose microfibrils can display amorphous and crystalline regions, various nanomaterials can be extracted by hydrolysis of the amorphous region, which are referred to as microcrystals, whiskers, nanocrystals, nanoparticles, microcrystallites, or nanofibers and can be collectively named cellulosic nanomaterials, nanocellulose or CNCs. Usually these materials have at least one of their dimensions in nanometer range (Habibi et al., 2010). CNCs are generally rigid rod-like nanoparticles obtained by controlled hydrolysis of cellulose fibers by acid. During acid treatment, large number of negative charges gets randomly distributed on the cellulose microfibril surface. Further mechanical or physical treatments disperse the charged microcrystallites aggregates into stable colloidal suspensions (Lima and Borsali, 2004).

Sources of CNCs

In principle, CNCs can be obtained from almost any cellulosic materials. Some of the major sources include plants, tunicates, bacteria, and algae.

Wood

Because of the widespread availability and high cellulose content, wood remains the first choice and most commonly used for the synthesis and production of CNCs. Trees are the main source of wood and it has been estimated that around 3 trillion trees are currently on our earth (Ehrenberg, 2015). Fibers derived from wood consist of large amount of helically spun cellulose microfibers impregnated with amorphous lignin and hemicellulose. However, production of pure CNCs from wood with dimension 1-100 nm generally requires extensive multistep processing and practice of harsh chemical and physical methods (Hubbe et al., 2008). Currently, CNCs are generally produced from "purified" wood, which is characterized by Kraft pulp and its ensuing dissolved pulp. One of the main advantages of using wood for the production of CNCs is the utilization of current pulp and paper industry infrastructure, minimizing the need for additional capital investment. However, for this process to be successful, purification and extraction of good quality cellulose remain essential prerequisites.

Bacteria

In addition to wood, bacteria can also be a source of high quality cellulose. Bacterial cellulose is extracellularly secreted by various species, mostly belonging to the following genera: *Gluconacetobacter, Rhizobium, Agrobacterium, Aerobacter, Achromobacter, Azotobacter, Sarcina*, and *Salmonella*. The most extensively studied cellulose producing bacterial species is *Gluconacetobacter xylinus* (Ross et al., 2001; Shoda and Sugano, 2005). In this species, the cellulose microfibrils are secreted by bacterial cells as an exopolysaccharide, mainly composed of water (99%) in which a network of cellulosic nanofibers with diameters ranging from 20 to 100 nm can be found (Klemm et al., 2011). Bacterial CNCs have very high crystallinity (~89%). Bacterial CNCs is allegedly a very pure form of cellulose with high weight-average molecular weight, excellent physical and mechanical properties such as high porosity and elastic modulus (Yoshinaga et al., 1997; Klemm et al., 2011; Lavoine et al., 2012). One of the main advantages of using bacterial cells for producing cellulose is the possibility of controlling microfibril production and crystallization through culture conditions, as shown by Chawla et al. (2008). However, mass scale production of bacterial cellulose for commercial utilization has yet to be demonstrated.

Tunicate

Tunicates are the only marine animals which are capable of producing cellulose microfibrils; these microfibrils are embedded in the protein matrix of the mantle (Kimura and Itoh, 1996). The epidermal membrane of tunicates contains cellulose-synthesizing enzyme complex mainly responsible for the synthesis of cellulose (Zhao and Lie, 2014). Although there are numerous species of tunicates, most of the research has focused on "sea squirts" (*Ascidiacea*). Tunicate cellulose microfibrils are similar to what is found in plant cell walls, and predominantly contain I_β allomorph. Tunicates cellulose displays an ultra-fine fibrous network with a very large aspect ratio, ranging from 3 to 67, (Peng et al., 2011), highly specific surface area fluctuating between 150 to 170 m^2/g, high crystallinity (95%), low density, and high mechanical strength and reactive surfaces (Sturcova et al., 2005; Zhao et al., 2015). The vastness of our marine ecosystem gives us promising reservoir for various kinds and amount of Tunicates CNCs, making them promising candidates for the production of cellulose nanocrystals for several innovative applications.

Algae

Algae, which are either unicellular or multicellular eukaryotes, contain chlorophyll as their primary photosynthetic pigment. Several algal species, such as *Valonia, Cladophora*, and *Boergesenia* are known to synthesize cellulose microfibrils in their cell wall (Mihranyan, 2011). Triclinic I_α allomorph is the major constituent of the algal cellulose. *Cladophora* has been reported to be one of the most important algal genera known to produce highly crystalline cellulose that does not adsorb moisture (Mihranyan et al., 2004). Due to differences in biosynthesis pathways between algal genera, considerable differences can be found in ensuing cellulose microfibril structures (Moon et al., 2011). Mainly, there are three groups, Groups 1, 2 and 3, of algae genera are based on their cell wall constituents (Nicholai and Preston, 1952). *Cladophorales*, and some members of *Siphonocladales* genera, belong to Group 1, displaying highly crystalline cellulos in their cell walls. Group 2 is found in green algae cell walls, which contain a large quantity of mercerized-like cellulose with low degree of crystallinity and decorated with randomly oriented cellulose chains (Mihranyan, 2011). *Vaucheria* and *Spirogyra* genera produce cellulose that belongs to Group 3, in which cellulose is not the major component of their cell wall (Mihranyan, 2011). The attention that an algae is attracting in terms of biomass production could be leveraged into algae being a source for biopolymer production as well as other novel uses.

CNC synthesis

Isolation of CNCs from initial cellulose raw materials consists primarily of two steps. The first step is pretreating the biomass for complete or partial removal of the matrix materials, such as hemicelluloses, lignin, fats, waxes, proteins, and inorganic contaminants, resulting in the isolation of the individual cellulose fibers. The second step is the controlled hydrolysis of the amorphous regions to segregate the crystalline part from the long cellulose polymer. Major processes used for the separation of CNCs are shown in Figure 3. Cellulose pretreatment and hydrolysis protocols need to be adjusted to fit the nature of the raw material that is being processed in order to obtain the desired cellulose nanocrystals with targeted morphological properties. Mainly there are three basic separation approaches, which include mechanical treatment, acid hydrolysis, or enzymatic hydrolysis. These approaches can be executed in tandem or separately in order to get the desired CNCs
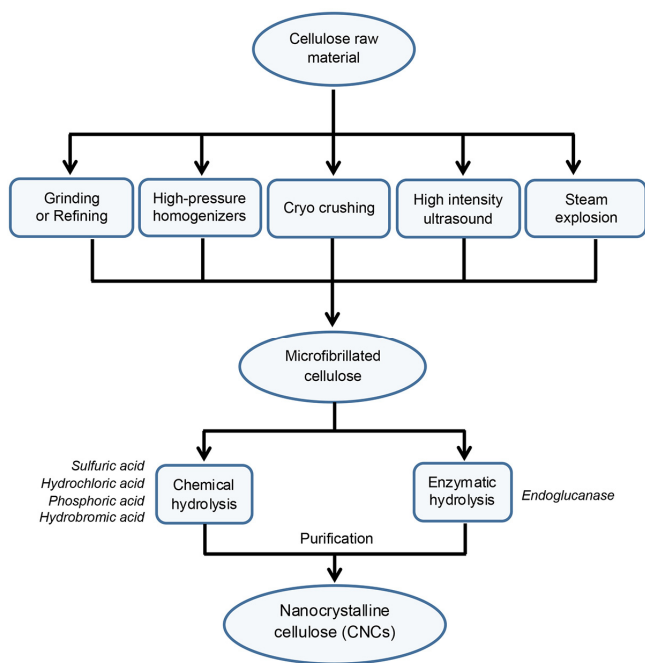
Figure 3. Schematic showing various methods and steps during the synthesis and the purifications of the CNCs starting from its raw source.

Figure 4. Probable CNC surface modifications: (a) sulphonation; (b) oxidation by TEMPO method; (c) esterification by acid chloride; (d) epoxidation; (e) esterification by acid anhydride; (f) urethane linkage by isocyanates; (g) silylation. Adopted with permission from Lam et al., 2012.

(Moon et al., 2011). Depending on the original source of the cellulose and preparation conditions, the geometrical length (L), width (W) and crystallinity of CNCs can vary widely. It has been reported that L × W dimensions of CNCs derived from hardwood, cotton linter, cotton, bacterial and tunicate cellulose were 140-150 nm × 4-5 nm, 25-500 nm × 6-70 nm, 70-300 nm × 5-11nm, 100-1,000 nm × 5-50 nm, and 100-3,000 nm × 10-30 nm, respectively (Habibi et al., 2010). Physical properties of CNCs from various sources are presented in Table 1. Unfortunately, CNCs are plagued with hydrophilicity and poor moisture resistance, making it essential to chemically modify the CNC surface (Figure 4). Chemical modifications of CNC surface are done mainly to increase its dispersibility within organic solvent or polymer resin along with improving its physicochemical properties.

Surface Modifications of CNCs

Noncovalent surface modifications

Primarily these methods take advantage of electrostatic adsorption of surfactants on the CNC surface to modulate the surface characteristics. Many ionic and non-ionic s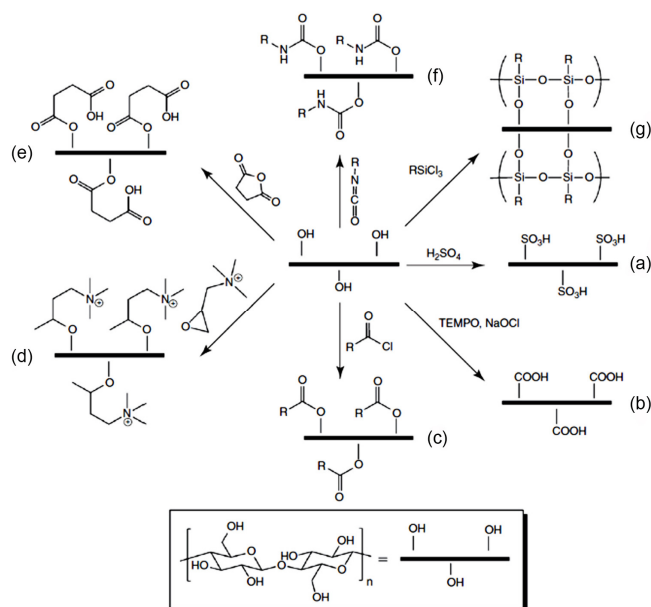urfactants such as mono and di-esters of phosphoric acid bearing alkylphenol tails (Heux et al., 2000); Beycostat A B09 and acid phosphate ester of ethoxylated nonylphenol (Bondeson and Oksman, 2007); sorbitan monostearate (Kim et al., 2009); xyloglucan oligosaccharide-poly (ethylene glycol)-polystyrene triblock copolymer (Zhou et al., 2009); cetyltetramethylammoniumbromide (CTAB) (Zhou et al., 2009) have been commonly used. As a substitute of negative charges on the CNC surface positive charges can also be introduced by use of various ammonium salts such as epoxypropyltrimethylammonium chloride (EPTMAC) (Hasani et al., 2008).

Covalent surface modifications

TEMPO-mediated oxidation

This method takes the advantage of selective oxidation of hydroxymethyl groups of polysaccharides into carboxylic group by 2, 2, 6, 6-Tetramethylpiperidine-1-oxyl (TEMPO) (de Nooy et al., 1994). This method is supposed to one of the environmentally friendly and easy to use (Habibi et al., 2010).

Esterification, silylation and other surface modifications

As CNCs contain numerous hydroxyl groups at the surface, chemical reactants which can easily react with

Table 1. Physicochemical properties of CNCs from various sources

Source	Length (nm)	Width (nm)	Aspect ratio	Predominant polymorph	Crystallinity	Reference
Algal (Valonia)	>1000	20	>500	Cellulose type-I	-	Sugiyama and Okano 1990; Hanley et al., 1992; Moon et al., 2011
Bacterial	100-1000	10-50	2-100	Cellulose type-I	72-74	Moon et al., 2011; Sacui et al., 2014
Cotton	70-300	5-11	10-42	Cellulose type-I	74-91	Araki et al., 2001; Miller and Donald, 2003; Teixeira et al., 2010; Morais et al., 2013
Flex	400	15-45	26.6-8.8	Cellulose type-I	87-89	Mondragon et al., 2014
Hard wood	140-150	4-5	37-28	Cellulose type-I	43-65	Beck-Candanedo et al., 2005; Moon et al., 2011
Hemp	580	20-50	29-11.6	Cellulose type-I	88-89	Mondragon et al., 2014
Jute	100–200	3-10	66.6-10	Cellulose type-I	69.72	Cao et al., 2012
Mengkuang leaves	50-400	5-25	10-20	Cellulose type-I	55.1-69.5	Sheltami et al., 2012
Parenchyma of oil palm trunk	892.86	10.51	84.9	Cellulose type-I	57.63	Lamaming et al., 2015
Pineapple leaf	249.7 ± 51.5	4.45 ± 1.41	60	Cellulose type-I	73	Santos et al., 2013
Rice straw	1000	125-497	8-2.1	Cellulose type-I	63.2-71.5	Jiang et al., 2013
Sisal	215 ± 67	5 ± 1.5	43	Cellulose type-I	78-79	Mondragon et al., 2014
Soft wood	100-150	10-20	5-15	Cellulose type-I	78-82	Beck-Candanedo et al., 2005; Li et al., 2011
Soy hulls	103.4-122.7	4.36-4.43	24.4- 29.4	Cellulose type-I	73.5	Neto et al., 2013
Spruce bark	175.3	2.8	63	Cellulose type-I	80	Normand et al., 2014
Switchgrass	148.1 ± 42.1	21.3 ± 4.3	11.2-4.1	-	69	Wu et al., 2013
Tomato peels	100–200	5-9	11-40	Cellulose type-I	80.8	Jiang and Hsieh, 2015
Tunicate	100-3000	10-30	300-3	Cellulose type-I	82.8-90.7	Peng et al., 2011, Habbibi et al., 2010; Sacui et al., 2014; Zhao et al., 2015
Vascular bundle of oil palm trunk	176.20	4.28	41.2	Cellulose type-I	63.91	Lamaming et al., 2015
White coir	172 ± 88	8 ± 3	22 ± 8	Cellulose type-I	82	Nascimento et al., 2014

hydroxyl groups have been commonly used to alter the surface chemistry and to attach various additional functionalities. Some of the commonly used attachment chemistry uses isocyanates, epoxides, acid halides, acid anhydrides and silanes, these chemical reactions can be extended further to generate numerous alternate surface chemistries and products such as amine, ammonium, alkyl, hydroxyalkyl, esters (Moon et al., 2011). While modifications are introduced, care is taken to preserve the original morphology of the CNCs.

Applications of CNCs

The unique biophysicochemical properties of CNCs have inspired many researchers to exploit them in various combinations to design materials with desired target properties. This has led to many exciting applications of CNCs (Figure 5). Potential applicability of CNCs is considered in biological, biomechanical, biochemical, and biophotonic sciences and engineering as well as in biomedical engineering.

Biological applications

Biomechanical: "Green" structural composite material

CNCs display various distinct properties, such as water solubility, high aspect ratio, elastic modulus, low density, strength, and ease of surface functionalization. Because of these unique properties, CNCs, used alone or in combination, can confer novel properties to base materials. Crystalline cellulose displays very good mechanical properties. Cellulose I has a Young's modulus of approximately 137 GPa (with intramolecular hydrogen bonding) and 92 GPa (without intramolecular hydrogen bonding), while cellulose II has a Young's modulus of 113 GPa (Mariano et al.,
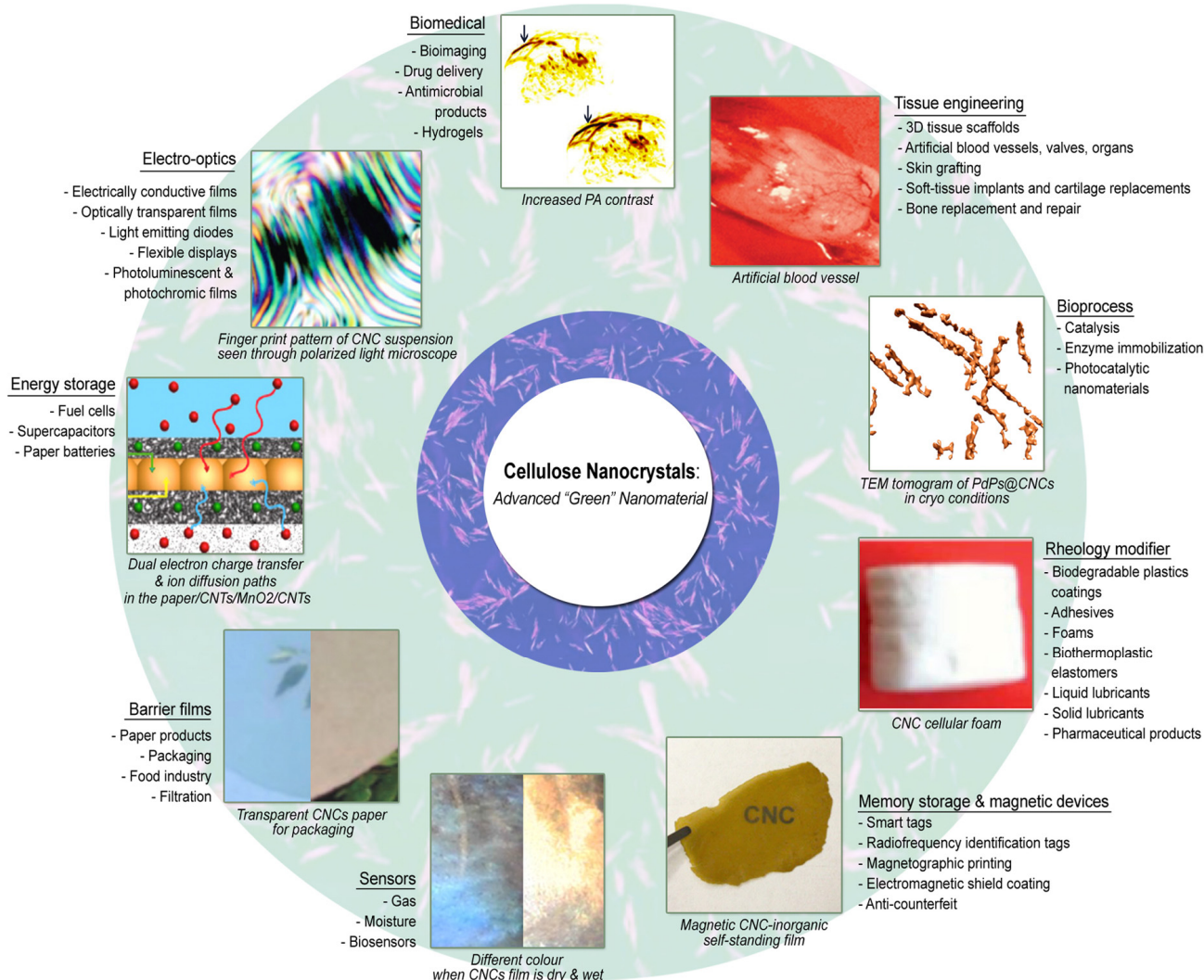
Figure 5. Schematic showing CNCs' potential applications for advanced "green" materials and devices. Adopted with permission from: Jokerst et al., 2014 (biomedical); Klemm et al., 2001 (tissue engineering); Kaushik et al., 2015 (bioprocess); Tasset et al., 2013 (rheology modifier); Nypelö et. al., 2014 (memory storage and magnetic devices); Zhang et al., 2013 (sensors); Nogi et al. 2009 (barrier films); Gui et al., 2013 (energy storage); Araki et al., 2000 (electro-optics).

2014). Compared with glass fibers, which has a Young's modulus of 70 Gpa and a density of 2.6 g cm^{-3}, crystalline cellulose displays a higher Young's modulus considering that the density for crystalline cellulose is approximately 1.5-1.6 g cm^{-3} (Mariano et al., 2014). The properties of crystalline cellulose are comparable to those of Kevlar, which has a Young's modulus of 60-125 GPA with a density of approximately 1.45 g cm^{-3} and to those of steel (200-220 GPa, density around 8 g cm^{-3}) (Mariano et al., 2014). The specific Young's modulus of cellulose crystals has found to be greater than the steel. Thus, by varying CNC composition through polymer matrix blending, physical properties such as robustness, flexibility, durability, weight and transparency could be tuned for various high-performance structural

applications (Zhou and Wu, 2012; Boufi et al., 2014). The tensile modulus and strength of polyacrylonitrile (PAN) polymer was found to be increased from 14.5 to 19.6 GPa and from 624 to 709 MPa respectively, as CNC loading increased from 0 to 10 (wt %) (Chang et al., 2015). With increasing CNC content (wt %) to polycaprolactone- based waterborne polyurethane (WPU) as the matrix from 0 to 30, the Young's modulus and tensile strength of the resulting composite increased from 0.51 to 344 MPa and 4.27 to 14.86 MPa, respectively (Cao et al., 2007). As an example, nanocellulose-based aerogels are considered to be an environment friendly alternative that could replace polystyrene foams. Nanocellulose-based aerogels are porous materials with high inner surface area, low density, good thermostatic properties, and have

good potential for uses such as insulation, particle filters, cushioning, and catalyst support.

Biochemical: "Green" rheology modifiers

CNC concentration is a critical parameter for conferring targeted rheological attributes of its suspensions (Shafiei-Sabet et al., 2012). By controlling the concentration of CNCs, it is possible to alter the rheological behavior of liquids, polymer melts, and particle suspensions. It has been found that the rheological properties of synthetic polymer like PAN changed significantly when cellulose nanocrystal was incorporated in the solution. The Newtonian fluid behavior of solution changed to shear-thinning fluid at lower angular frequency (Chang et al., 2015). Rheological control is a prerequisite for CNC applications in paints, adhesives, lacquers, food, cosmetics, pharmaceutical, and other industrial products. CNCs have potential, in pharmaceutical applications, as candidates for drug formulations and delivery systems. Pharmaceutical products, such as creams, ointments, and lotions, are generally emulsions or suspension type systems (Mastropietro et al., 2013). Therefore, the rheology of the carrier system plays a crucial role in the delivery and efficacy of the administered drug. Moreover, due to large surface area and higher density of charged groups, CNCs offer high compaction and dosing properties, where the CNC surface can be modified for modulating the loading capacity and release of the active ingredients (Jackson et al., 2011).

Biochemical: "Green" barrier films

The possibility of tailoring CNC surface chemistry and spacing, combined with its inherently high strength, have attracted interest for its use in the development of barrier films. CNC-based barrier films have potential applications in batteries, filtration devices, and packaging, and paper products (Khan et al., 2012; Zhou and Wu, 2012; Lalia et al., 2013). These CNC-based packaging materials could be used for prolonging the shelf-life of pharmaceutical, food and drink products, protecting against physical, biochemical, and microbiological degradation and deterioration (Nair et al., 2014). To be effective, CNC-based packaging materials should provide sufficient mechanical strength, barrier against air, water vapor, light, microorganisms, and external contaminants (Spence et al., 2011). Due to extensive hydrogen bonding, the dense CNC networks decrease the permeability within the CNC-based films or composites, making it difficult for the gas and other external molecules to pass through. Furthermore, due to size and swelling constraints, CNCs have strong inhibitory effect on water vapor diffusion (Nair et al., 2014). The major advantage lies in the tunability of the CNCs' barrier properties, which can be obtained by changing the packing density. These tunable CNC properties may be beneficial for the production of customized materials (Rodionova et al., 2011).

Biophotonic: "Green" electro-optic devices

The electro-optic effect of a material is the change of the refractive index, caused by an electric field. This phenomenon has found a number of applications in optical devices, such as electro-optic sensors based on ring microresonators, liquid crystal displays (LCDs), Q-switches for lasers, spatial light modulators, optical shutters, and variable density filters (Dalton et al., 2010). The three-dimensional (3D) hierarchical structures of CNCs at various scales and their ability to integrate other functional materials make CNC-based products promising candidates for electrical, electrochemical, and optical devices (Zheng et al., 2013). The anisotropic rod-like morphology of CNCs promotes lyotropic liquid crystalline behavior, which can be modified through concentration modulations (Marchessault et al., 1959; Urena-Benavides et al., 2011; Lagerwall et al., 2014). Under certain concentration and conditions, CNC suspensions may be slowly evaporated, resulting in semi-translucent films with ordered chiral nematic liquid crystals. The latter display iridescence reflecting polarized light in narrow wavelength ranges, which are governed by the chiral nematic pitch and the refractive index of the film (Dufresne, 2013). The helical liquid crystalline self-assembly of CNCs provides chirality to the added material and more sensitivity to circular polarization. CNCs can also induce similar type of ordering in polymeric macromolecules such as alginate or inorganic materials like silica when mixed together (Shopsowitz et al., 2010; Urena-Benavides et al., 2010). The optical properties of CNC film dispersions can be modulated by controlling the cholesteric pitch, which in turn can be influenced by dispersion composition, polyelectrolyte, temperature, and shear. It has been found that incorporation of polyelectrolyte layers can change the colour and reflectiveness of CNC-based materials (Cranston and Gray, 2006; Podsiadlo et al., 2007). Moreover, manipulating the packing density results in regulation of the interstices between the fibers and avoids light

scattering, which leads to regulated transparency, while maintaining the original high performance qualities (Nogi et al., 2009). Electrospun cellulose-based CNCs and nematic liquid crystal composite system has shown promising tunability of light transmission coefficients from 1-89% (Almeida et al., 2010). The 3D hierarchical structure, porosity and electrolyte absorption properties of cellulose fibers can be exploited for many advanced energy devices. Recently, composites made of combinations of cellulose, carbon nanotubes, and manganese dioxide demonstrated superior supercapacitive performance (Gui et al., 2013). The interconnected porosity provided good diffusion channels, facilitating fast access of ionic species to the electrode surfaces (Zheng et al., 2013). These excellent properties of CNCs can benefit the development of a variety of new advanced biophotonic devices such as variable density optical filters, light valves, and liquid display devices.

Biomedical applications

The CNCs' low toxicity and minimal risk to the environment (i.e., low ecotoxicological risk), combined with their unique physicobiochemical characteristics, place them as promising materials for biomedical applications. It has been only recently that these CNC-based nanoscale materials have been considered for biomedical applications. CNC-based nanoscale materials are very appealing due to the fact that there is an increasing demand for "green" and biocompatible functional materials.

Tissue engineering: "Green" tissue scaffolds

Tissue engineering is an alternative or a complementary solution to organ failure or to diseased organs by supporting the growth of natural, synthetic, or semisynthetic tissues that can mimic the natural organization and function of organs; these implants are either fully functional from the start, or grow into the required functionality after being grafted inside the body (Persidis, 1999). Tissue engineering is based on the fact that living systems, through growth, differentiation and organization, have the ability to repair and regenerate damaged tissues. In *in vivo* circumstances, various physiological and microenvironmental cues affect cells, regulating their behavior, differentiation, growth, and outcome (Lutolf et al., 2005; Pérez et al., 2013). These physiological cues can be initiated by extracellular matrix (ECM), proteins, various bioactive ingredients, and neighboring cells (Domingues, 2014). In tissue engineering, it is important

for any implanted scaffold to mimic the ECM, which displays properties that can actively promote the natural healing and self-repair capacity of the body (Place et al., 2005). The hierarchical arrangement of the ECM varies from nano to macro scale; because it is based on tissue type and functions the matrix differs in composition and spatial organization of their respective components, making development of artificial scaffolds more challenging (Kim and Deaton, 2013; Kim et al., 2014). The surface characteristics of scaffolds, such as roughness, topography, porosity, pore size, pore interconnectivity, surface area to volume ratio, and chemistry, all play a pivotal role in tissue engineering (Domingues et al., 2014). Though it is very difficult to mimic the natural ECM environment, various biodegradable and bioactive materials, along with fabrication methodology, have been explored for the development of suitable scaffolds that mimic natural ECMs, such that the attachment, migration, proliferation and differentiation of cells can be facilitated, resulting in desired cellular arrangements (Place et al., 2005). Currently, more focus has been given in developing nanocomposites in order to better mimic the natural ECM hierarchical structure. For external implanted scaffolds, it is important to have cell friendly environments that foster cell attachment and proliferation. The distinctive features of CNCs, which include excellent biocompatibility, biodegradability, high mechanical strength, ability to integrate various reactive functional groups, hydrophilicity, low cost, and renewable nature, make it a promising material for tissue engineering. Various natural polymers, such as, chitosan, gelatin, silk collagen, and other synthetic materials have been used in different combinations with CNCs to develop effective scaffolds with improved physical and biological functions. Blending CNCs and silk fibroin composite films resulted in interesting and novel materials (Noishiki et al., 2002). Silk fibroin-microcrystalline cellulose composite films showed increases in tensile strength and ultimate strain, by up to five folds, when compared to those of native fibroin or cellulose films. In bone tissue engineering, it has been a challenge to create load-bearing scaffolds, where polymer-based scaffolds often display low mechanical strength. Compared to other reinforcing materials, CNC-based materials show good mechanical properties, low extension to break, high aspect ratios, high surface area, and good biocompatibility. The use of CNC-based materials has become well-like in bone tissue engineering applications. Recently, bio-nanocomposite scaffolds, using human adult

adipose derived mesenchymal stem cells (hASCs), maleic anhydride grafted poly lactic acid and CNCs has been developed for bone tissue engineering applications (Zhou et al., 2013). *In vitro* study of cellulose-based porous 3D scaffolds, with mechanical properties in the mid-range of human trabecular bone, promoted positive proliferation and differentiation of human osteoblasts (Kumbar et al., 2011). Hydroxyapatite CNC membranes have also been seen to accelerate new bone formation at the defected sites in rat tibiae, whereas goat bone apatite and CNC composite stimulated bone cell differentiation and proliferation (Tazi et al., 2012; Fan et al., 2013). An encouraging step towards conceptualization of CNCs in tissue engineering was observed wherein the myoblasts cells were able to recognize the CNC topography to position itself along the CNC bulk direction and fuse to form highly oriented multinuclear myotubes. This was possible when radially oriented submonolayer surfaces of high aspect ratio CNCs onto flat glass substrates were used to grow the respective cells (Dugan et al., 2010). Similar effects were seen with C2C12 skeletal muscle myoblasts, where relative orientation of CNCs guided the growth, fusion, and terminal differentiation of the cells (Dugan et al., 2013). For skin tissue engineering, CNCs have been studied to improve the mechanical properties of collagen. It has been observed that collagen-CNC composites are biocompatible and have no side effect on cell morphology, viability or proliferation (Li et al., 2014). Gelatin microspheres (GMs), containing basic fibroblast growth factor (bFGF) and porous collagen/CNC scaffolds, were incubated with human umbilical vein endothelial cells, and showed significant increases in cell proliferation. In *in vivo* studies, where the above mentioned scaffolds were implanted subcutaneously into Sprague-Dawley rats, the results showed significant increases in the number of newly formed and mature blood vessels (Li et al., 2014). Combinations of silk fibroin and CNCs have shown that significant increases in cell adhesion and proliferation (Barud et al., 2014), whereas CNC pectin and carboxymethyl cellulose composite were demonstrated to control water uptake mechanisms (Ninan et al., 2013). Efforts are currently underway to develop CNCs and heparin nanofibrous scaffold with anticoagulant properties for their potential use in vascular tissue engineering (Wan et al., 2011). Chondrocyte-packed CNC nanocomposites, when treated in cultured medium containing combination of insulin-like growth factor-1 and transforming growth factor-beta1,

showed increases in mRNA expression for collagen type II and aggrecan. There was increase in total collagen and sulfated-glycosaminoglycans production leading to increased net tissue weight, as well as expression of cartilage-associated genes, including collagen types II and IX, cartilage oligomeric matrix protein, and aggrecan (Li et al., 2008). Hydrogels, derived from CNCs, can provide appropriate micro environment and mechanical support for the differentiation and growth of cells. It has been observed that CNC hydrogels have positive effect on the differentiation of the human hepatic cell lines (HepG2 and HepaRG), and spheroid formation of cells (Bhattacharya et al., 2012). CNC-based biocomposites have also been studied for the rapid tissue regeneration and capillary formation around wound areas. Microbial cellulose accelerated wound healing by reducing inflammation and increasing collagen deposition as well as increasing neovascularisation (Park et al., 2014). Recently, catalase, containing CNCs and calcium peroxide nanocomposite, has been found to be effective in increasing the L-929 fibroblasts cells density and showed potential for accelerating wound healing and sterilization (Chang and Wang, 2013). Three-dimensional starch-CNCs with controlled porosity, mechanical strength, and biodegradability have also been shown to support and promote growth of fibroblast cells (Nasri-Nasrabadi et al., 2014). The above examples show that CNCs have great potential to be used for engineering highly ordered tissues and repair the damaged or diseased portion of the body.

Bioimaging: "Green" contrast agents

Imaging modalities with high sensitivity and selectivity, spatial resolution, and good depth penetration play an important role in the screening, diagnosis, planning, and therapy monitoring of several types of chronic diseases. Basically, it can facilitate better personalized medicine and clinical management for any clinical manifestations. For the past few decades, efforts have been made to develop a non-ionizing and non-invasive techniques that can be used for the early and accurate detection of various cancers. Ultrasound-guided photoacoustics and phothermal imaging have emerged as promising techniques. With recent developments in various targeted contrast agents and photoacoustic (PA) technique, real time *in-vivo* molecular imaging is possible for better molecular and cellular characterization of cancer cells (de la Zerda et al., 2011; Kim et al., 2013, 2014b). In PA imaging, contrast is

generated by converting light pulses into an acoustic signal. Basically, when tissues are exposed to laser light, they absorb the laser energy and undergo rapid thermoelastic expansion, leading to the generation of ultrasound waves. These ultrasound waves are detected by transducer converting the mechanical acoustic waves into electric signals. The captured electric signals are then processed to form an image (Mallidi et al., 2011). Thermoacoustic imaging is another emerging modality. It is an application of the PA effect where imaging is done through an excitation source, mainly involving far-infrared light or microwaves. These modalities offer longer imaging depth. Many synthetic materials have been used as contrast agents to improve signals and depth; examples include metal oxides, methylene blue, indocyanine green, fluorophore, graphene, fluorescent proteins, quenchers, quantum dots and nanoparticles (Wu et al., 2014). While some of the contrast agents applied in various imaging modalities offers high potential for good molecular imaging, they remain toxic with limited biodegradability, limiting their possibility of wide applications. Recently, the use of cellulose-based nanoparticles has been explored in PA applications to improve imaging capability. CNC-based composite enhanced PA signals in live mice and was also able to undergo biodegrading *ex vivo* in the presence of a naturally occurring enzyme (Jokerst et al., 2014). Although CNCs are biocompatible, nontoxic to the human body, and enhance imaging potential, their use has yet to be expanded. Most of the time, the contrast agents or other imaging molecules are coupled with the carrier molecule. For biological imaging applications, it is essential that these molecules should offer desired biodistribution for the effective delivery to the targeted tissue, and adequate rate of clearance from the body. To be characterized as an acceptable carrier molecule, they should be small, natural, and have neutral or hydrophilic surface. Interestingly, CNCs display the properties of good carrier molecules. Also, by exploiting the selective carbohydrate/protein-carbohydrate interactions, CNC-based imaging or contrast agents can be developed for specific receptor sites on the specific cells, tissues, and organs for *in vivo* imaging, sensing and tracking. Efforts have been taken to develop fluorescein-5'- isothiocyanate covalently attach to the surface of CNCs for various fluorescence techniques, like spectrofluorometry, fluorescence microscopy and flow cytometry (Dong and Roman, 2007). By modifying the cellulose nanocrystals with 2,2′:6′,2″-terpyridine, followed by supramolecular assembly of terpyridine-modified

perylene dye into the terpyridine-modified cellulose nanocrystals, a highly fluorescent nanocellulosic composite was prepared via RuIII/RuII reduction for potential bioimaging (Hassan et al., 2012). Recently, for imaging purposes, most of the studies have been focused on functionalization of various gold and magnetic nano-particles, carbon nanotubes (CNTs), graphene, silica or quantum dots with glucose (molecular unit of CNCs) (Zharov et al., 2005; de la Zerda, 2011; Kim and Deaton, 2013; Kim et al., 2013, 2014b; Kotagiri and Kim, 2014; Hao et al., 2015). Glucose-coated gold nanoparticles with blood-brain barrier-permeable (BBB) neuropeptides have displayed interesting BBB permeability and bio-distribution, increasing the candidacy as a good positron emission tomography (PET) contrast agent for *in vivo* imaging of brain (Frigell et al., 2014). Silica-coated iron oxide core shell magnetic nanoparticle, functionalized with carbohydrate, have been used for *in vivo* imaging of brain, spleen, and liver through magnetic resonance imaging (MRI) (Farr et al., 2014). Multifunctional CNC conjugates, prepared using a quinolone fluorophore and carbohydrate ligands, have recently been studied for biorecognition of carbo-hydrate-binding proteins and bacterial imaging. These nano composites could selectively recognize cognate lectins and selectively interact with FimH-presenting *Escherichia coli* cells (Zhou et al., 2015). Though CNC-based imaging still remains to be explored, it has shown great potential to become a good contrast agent. With proper modifications and conjugation, it can be developed into highly specific and selective imaging and tracking agents for the cells and tissues in real time.

Challenges and Future Directions

Undoubtedly, cellulose nanocrystals have shown enormous potential for the development of a next generation advance materials and devices. Contemporary reports and research developments on CNCs have led to remarkable discoveries with promising potential awaiting to come in the near future. Further comparison and extensive investigation on the properties of CNCs, derived from different sources and methodology, will certainly determine their respective broader applications. However, there are many hurdles to overcome prior to having CNCs become part of various technologies and devices. Most of the properties of cellulose fibers are due to strong inter- and intra-particle

hydrogen bonding, which may be perturbed by the nano-scale effect. The first challenge comes early, during the processing of the cellulosic materials itself. Due to strong adhesion property between the cellulose fibers, it is difficult to produce homogenous nanoscale cellulose. The challenges remain in obtaining consistent homogeneous dispersion of CNCs for many of the composite preparations and applications. CNCs have a strong tendency to agglomerate during isolation and processing. Dispersion of hydrophilic CNCs in hydrophobic matrices is another big challenge. CNCs are prone to hornification (co-crystallisation) during drying and form large nanocellulose agglomerates. These large agglomerates are very difficult to disperse in hydrophobic materials, leading to poor composition and performance of the resulting nanocomposites. The extensively available hydrogen bonds on the surface of CNCs are the keys for determining the future and applicability of CNCs for the development of nano-composites. The synthesis of new materials and their applications will be strongly dependent on the surface properties of CNCs and their compatibility with the matrix in which they are processed. More research is needed to fully understand the adhesion properties of CNCs, including mechanical interlocking, interpenetrating networks, covalent linkages, and interfacial properties in addition to the hydrogen bonding mechanisms, so that we can create CNCs that will be compatible with bio-polymers, thermosets and thermoplastics. One of the prerequisites to synthesize CNC-based composite polymers is to chemically modify or derivatize the surface of CNCs. The chemical modifications and derivatization may also influence the properties of the final product. Proper methodology for controlling the level and type of functional modifications on the CNC surface has to be developed for specific applications. Despite the con-siderable advancement in surface modifications, proper tailoring of the functionality of the CNC surface for homogeneous dispersion within polymer matrices is still one of the major challenges. CNCs have shown to have promising properties, yet they are lagging behind most of their synthetic counterparts. Young's modulus, being higher than glass fibers, CNCs and their composites have yet to be established as glass fibers' alternative. Extensive fiber degradation, during compounding/extrusion in the course of composite formation and time/temperature dependent mechanical properties, is a prime limitation in exploiting the full potential of CNCs. Cost effectiveness is another important factor for the commercialization of any product. Many of the synthetic products have lower input cost than CNC-based materials. It is less expensive to produce polystyrene-based aerogels, through blowing gas in large scale, than freeze drying methods for the synthesis of CNC aerogels. Regularity and continuous alignment of CNCs for many nanoscale phenomenon and application is very crucial. We still need much more work in developing suitable methodology to achieve greater control over homogeneous alignment; positioning and interfacial compatibility of nanocomposites to maximize the properties of CNC-based materials. Specifically, for probable application in tissue engineering, CNC-based scaffolds should meet a number of requirements. Depending on the physiological and anatomical functions, different tissues vary in their mechanical structure and functionality. Synthetic scaffolds should have properties sufficiently enough for their fixation at proper site in the body, at least closely mimic the natural environment, i.e. different CNC-based scaffolds for different tissues. This will require fine tuning of the various properties of CNCs. A good scaffold should have optimal, well-designed 3D pore size with sufficient surface area, mechanical strength with an adequate self-life, a resistance against stricture, inter-connected micropores, and compatible absorption kinetics. These properties are important for optimum cell seeding and survival of the cells, vascular formation, transport of oxygen and waste materials, and optimum supply of nutrients. However, most of the current CNC scaffolds offer less controlled pore sizes for proper cell seeding and survival of the growing cells and they are also prone to degradation and distortion before the completion of tissue regeneration. Most of the current studies and developments in CNC-based scaffolds are focused on the reinforcement effect of the CNCs to nanocomposites. We need more intensive *in vivo* studies on the mechanisms of nanocellulose interaction with the cells and their sur-rounding environment. Biocompatibility, i.e. the ability to remain in contact with living without invoking immune response, cytotoxicity, or other side effects are some of the prime prerequisites for any exogenous material to be introduced to the living system. We need much more experimental evaluations regarding cellular toxicity before fully comprehending CNCs as sources for biomedical applications. Regulated hydrophobicity and hydrophilicity of CNCs surface is also an important factor to consider for the proper adherence to the cells, i.e. we need proper

functionalization process and methodology to tune the surface hydrophobic and hydrophilic properties so that proper cell adherence can be achieved. Furthermore, study on regulated behavior of cells through controlling the morphology and the physical structures of CNCs will ensure better crafting and development of promising CNC-based materials for tissue engineering. So far, for imaging and sensing purposes, the CNC-based materials have been fairly simple and nonspecific, in comparison to the complex and unique carbohydrate chemistry of the biological cells and tissues. Biological cells are rich in carbohydrates and the properties and characteristics vary depending upon the cell type. It is possible to design specific types of CNC-based materials to mimic and interact with various cells or tissues. Possibilities of introducing multiple functional groups on the CNC surface make them better choice to develop multivalent materials for binding to the cell receptors with greater affinity and specificity with tailored sensing properties. The cell status could thus be analysed more precisely and efficiently. New strategies are thus needed for making more tissue or cell specific imaging and sensing agents. This will require wide diversity and sophisticated control in maintaining spatial distribution, arrangements, and density of the functionalities on the surface of CNCs, as well as placement of various external metallic of non-metallic particle or molecules to enhance the properties. This will ultimately result in controlled modulation of the affinities and specificities of the resultant composites to suit various bioimaging and biosensing modalities. The success of CNCs for future applications will depends on how well and easily CNCs can be manipulated and integrated with other allied materials and systems. The principal aim of developing advanced materials and technology is to generate a new broad spectrum and more efficient system than contemporary counterparts. It is necessary to define and tailor the properties of CNCs and their composites, according to necessity and choice. Anisotropic assembly of CNCs alone or with the impregnated constituents will be one the prime requirement for such advanced developments. Coaxial electrospinning method is one of the emerging techniques through which multifunctional CNC fibers can be produced. It has been reported that assembled multifunctional fibers can respond to multiple stimuli at a time with individual cores having different physical properties, such as photonic crystal selective reflection from one core and regular birefringence

with another core, and having dissimilar responses to changes in temperature (Kye et al., 2015). Layer-by-layer assembly (LBL) is another technique to control multilayer production. However, overall control of the integrity of the final structure and manipulation of functionality need further research and evaluation. The nanotoolbox technology (Kim et al., 2011; Kim et al., 2012; Kim and Deaton, 2013; Kim et al., 2013; Kim and Tung, 2015) is one of the promising methods. It allows different nanoparticles and nano-building blocks to assemble in predefined spatial arrangements. Hence, one can deliberately functionalize target molecules at an aimed destination and construct a highly controlled architecture at the molecular level. The successful anisotropic design can reap vast rewards in CNC applications and efficiencies, whether it is opto-electronics, nanotheranostics, or biomedical applications. Overall, creating control over the properties, shapes, size, and structure, integration of external materials at specific locations and spatial orientation, cost effectiveness, reliability and reproducibility of the synthesis methods will be crucial and beneficial to pave the way for dependable commercial applications of CNCs and its composites. Although, there are many challenges and hurdles to overcome, once we get control over manipulating the properties, designing and assembling, these CNC-based materials will pave a new era in modern technology and devices.

Conclusions

Cellulose, despite being the most abundant natural polymer with unique physicochemical properties, has only quite recently gained prominence as a renewable resource of sustainable "green" material in the form of nanoscale cellulose crystals. Cellulose nanocrystals are now widely affecting modern technological advancements. CNCs and their composites offer answers to some intriguing questions of sustainable development and environmentally friendly technology. Many breakthroughs and potential applications have emerged from the research and discovery of novel properties of the CNCs themselves and their composites. The remarkable mechanical strength, lyotropic liquid crystalline behavior, excellent biocompatibility, biodegradability, and hydrophilicity with various chemical functionalization properties have provided a rich suite and platforms for synthesis of new materials and composites

with useful and unexpected properties. Although, we described and discussed only few selected examples of CNC research, a number of other studies have, by now, shown the emerging potential in the field of drug-delivery systems, biomedical applications, tissue engineering, bioimaging, energy storage, biophonotics, and smart polymers. The continuously increasing numbers of new applications in various fields is envisaging CNCs' great potential to become sustainable sources for commercial production of many advanced "green" materials and devices.

Conflict of Interest

The authors have no conflicting financial or other interests.

Acknowledgments

References

Almeida, P. L., S. Kundu, J. P. Borges, M. H. Godinho and J. L. Figueirinhas. 2009. Electro-optical light scattering shutter using electrospun cellulose based nano and microfibers. Applied Physics Letters 95(4):043501-043504.

Araki, J., M. Wada and S. Kuga. 2001. Steric stabilization of a cellulose microcrystal suspension by poly(ethylene glycol) grafting. Langmuir 17(1):21-27.

Araki, J., M. Wada, S. Kuga and T. Okano. 2000. Birefringent glassy phase of a cellulose microcrystal suspension. Langmuir 16(6):2413-2415.

Aulin, C., S. Ahola, P. Josefsson, T. Nishino, Y. Hirose, M. Osterberg, et al. 2009. Nanoscale cellulose films with different crystallinities and mesostructures-their surface properties and interaction with water. Langmuir 25(13):7675-7685.

Barud, H. G. Oliveira., H. da S. Barud, M. Cavicchioli, et al. 2015. Preparation and characterization of a bacterial cellulose/silk fibroin sponge scaffold for tissue regeneration. Carbohydrate Polymers 128:41-51.

Beck-Candanedo, S., M. Roman and D. G. Gray. 2005. Effect of reaction conditions on the properties and behavior of wood cellulose nanocrystal suspensions. Biomacromolecules 6(2):1048-1054.

Bhattacharya, M., M. M Malinen, P. Lauren, Y.-R. Lou, S. W. Kuisma, L. Kanninen, et al. 2012. Nanofibrillar cellulose hydrogel promotes three-dimensional liver cell culture. Journal of Control Release 164(3):291-298.

Bondeson, D. and K. Oksman. 2007. Dispersion and characteristics of surfactant modified cellulose whiskers nanocomposites. Composite Interfaces 14(7-9):617-630.

Boufi, S. 2014. Nanofibrillated cellulose: sustainable nanofiller with broad potentials use. In: Biomass and Bioenergy eds. K. R. Hakeem, M .Jawaid and U. Rashid, pp. 267-305. Springer International Publishing Switzerland.

Brinchi, L., F. Cotana, E. Fortunati and J. M. Kenny. 2013. Production of nanocrystalline cellulose from lignocellulosic biomass: Technology and applications. Carbohydrate Polymers 94(1):154-169.

Cao, X., B. Ding, J. Yu and S. S. Al-Deyab. 2012. Cellulose nanowhiskers extracted from TEMPO-oxidized jute fibers. Carbohydrate Polymer 90(2):1075-1080.

Cao, X., H. Dong and C. M. Li. 2007. New nanocomposite materials reinforced with flax cellulose nanocrystals in waterborne polyurethane. Biomacromolecules 8(3): 899-904.

Chang, C.-W. and M.-J. Wang. 2013. Preparation of micro-fibrillated cellulose composites for sustained release of H_2O_2 or O_2 for biomedical applications. ACS Sustainable Chemical Engineering 1(9):1129-1134.

Chang, H., A.-T. Chien, H. C. Liu, P.-H. W. Wang, B. A. Newcomb and S. Kumar. 2015. Gel spinning of poly-acrylonitrile/cellulose nanocrystal composite fibers. ACS Biomaterials Science & Engineering 1(7):610-616.

Chawla, P. R., I. B. Bajaj, S. A. Survase and R. S. Singhal. 2009. Microbial cellulose: Fermentative production and applications. Food Technology and Biotechnology 47(2):107-124.

Chen, H. 2014. Chemical composition and structure of natural lignocellulose. In: Biotechnology of Lignocellulose: theory and practices, pp. 25-71. Springer Netherlands.

Chinga-Carrasco, G. 2011. Cellulose fibres, nanofibrils and microfibrils: the morphological sequence of MFC components from a plant physiology and fibre technology

point of view. Nanoscale Research Letter 6(1):417.

Cranston, E. D. and D. G. Gray. 2006. Morphological and optical characterization of polyelectrolyte multilayers incorporating nanocrystalline cellulose. Biomacromolecules 7(9):2522-2530.

Dalton, L. R., P. A. Sullivan and D. H. Bale. 2010. Electric field poled organic electro-optic materials: State of the art and future prospects. Chemical Reviews 110(1): 25-55.

de la Zerda, A., J.-W. Kim, E. I. Galanzha, S. S. Gambhir and V. P. Zharov. 2011. Advanced contrast nanoagents for photoacoustic molecular imaging, cytometry, blood test, and photothermal theranostics. Contrast Media & Molecular Imaging 6:346-369

de Nooy, A. E. J., A. C. Besemer and H. van Bekkum. 1994. Highly selective tempo mediated oxidation of primary alcohol groups in polysaccharides. Recueil des Travaux Chimiques des Pays-Bas 113(3):165-166.

Domingues, R. M., M. E. Gomes and R. L. Reis. 2014. The potential of cellulose nanocrystals in tissue engineering strategies. Biomacromolecules 15(7):2327-2346.

Dong, S. and M. Roman. 2007. Fluorescently labeled cellulose nanocrystals for bioimaging applications. Journal of American Chemical Society 129 (45):13810-13811.

Duchesne L. C. and D. W. Larson. 1989. Cellulose and the evolution of plant life. BioScience 39(4):238-241.

Dufresne, A. 2013. Nanocellulose: A new ageless bionanomaterial. Materials Today 16(6):220-227.

Dugan, J. M., J. E. Gough and S. J. Eichhorn. 2010. Directing the morphology and differentiation of skeletal muscle cells using oriented cellulose nanowhiskers. Biomacromolecules 11(9):2498-2504.

Dugan, J. M., R. F. Collins, J. E. Gough and S. J. Eichhorn. 2013. Oriented surfaces of adsorbed cellulose nanowhiskers promote skeletal muscle myogenesis. Acta Biomaterialia 9(1):4707-4715.

Ehrenberg, R. 2015. Global count reaches 3 trillion trees. Nature doi:10.1038/nature.2015.18287.

Eichhorn S. J. and G. R. Davis. 2006. Modelling the crystalline deformation of native and regenerated cellulose. Cellulose 13(3):291-307.

Fan, X., T. Zhang, Z. Zhao, H. Ren, Q. Zhang, Y. Yan and G. Lv. 2013. Preparation and characterization of bacterial cellulose microfiber/goat bone apatite composites for bone repair. Journal of Applied Polymer Science 129(2):595-603.

Farr, T. D., C. H. Lai, D. Grünstein, G. Orts-Gil, C. Wang, P. Boehm-Sturm, P. H. Seeberger and C. Harms. 2014. Imaging early endothelial inflammation following stroke by core shell silica superparamagnetic glyconanoparticles that target seletin. Nano Letters 14(4): 2130-2134.

Frigell, J., I. García, V. Gómez-Vallejo, J. Llop and S. Penadés. 2014. ^{68}Ga-labeled gold glyconanoparticles for exploring blood-brain barrier permeability: preparation, biodistribution studies, and improved brain uptake via neuropeptide conjugation. Journal of American Chemical Society 136(1):449-457.

Gui, Z., H. Zhu, E. Gillette, X. Han, G. W. Rubloff, L. Hu and S. B. Lee. 2013. Natural cellulose fiber as substrate for supercapacitor. ACS Nano 7(7):6037-6046.

Habibi, Y., L. A. Lucia and O. J. Rojas. 2010. Cellulose nanocrystals: chemistry, self-assembly and applications. Chemical Review 110(6):3479-3500.

Hanley, S. J., J. Giasson, J.-F. Revol and D. G. Gray. 1992. Atomic force microscopy of cellulose microfibrils: Comparison with transmission electron microscopy. Polymer 33(21):4639-4642.

Hao, N., K. Neranon, O. Ramström and M. Yan. 2015. Glyconanomaterials for biosensing applications. Biosensors and Bioelectronics. doi:10.1016/j.bios.2015.07.031.

Hasani, M., E. D. Cranston, G. Westmana and D. G. Gray. 2008. Cationic surface functionalization of cellulose nanocrystals. Soft Matter 4:2238-2244.

Hassan, M. L., C. M. Moorefield, H. S. Elbatal, G. R. Newkome, D. A. Modarelli and N. C. Romano. 2012. Fluorescent cellulose nanocrystals via supramolecular assembly of terpyridine-modified cellulose nanocrystals and terpyridine-modified perylene. Materials Science and Engineering: B 177(4):350-358.

Heux, L., G. Chauve and C. Bonini. 2008. Nonflocculating and chiral-nematic self-ordering of cellulose microcrystals suspensions in nonpolar solvents. Langmuir 16 (21): 8210-8212.

Hubbe, M. A., O. J. Rojas, L. A. Lucia and M. Sain. 2008. Cellulosic nanocomposites: A review. BioResources 3(3):929-980.

Jackson, J. K., K. Letchford, B. Z. Wasserman, L. Ye, W. Y. Hamad and H. M. Burt. 2011. The use of nanocrystalline cellulose for the binding and controlled release of drugs. International Journal of Nanomedicine 6:321-330.

Jarvis, M. 2003. Cellulose stacks up. Nature 426:611-612.

Jiang, F. and Y.-L. Hsieh. 2015. Cellulose nanocrystal

isolation from tomato peels and assembled nanofibers. Carbohydrate Polymers 122:60-68.

Jiang, F., S. Han and Y.-L. Hsieh. 2013. Controlled defibrillation of rice straw cellulose and self-assembly of cellulose nanofibrils into highly crystalline fibrous materials. RSC Advances 3:12366-12375.

John, M. J. and S. Thomas. 2008. Biofibres and biocomposites. Carbohydrate Polymers 71(3):343-364.

Jokerst, J. V., D. Van de Sompel, S. E. Bohndiek and S. S. Gambhir. 2014. Cellulose nanoparticles are a biodegradable photoacoustic contrast agent for use in living mice. Photoacoustics 2(3):119-127.

Kalia, S., A. Dufresne, B. M. Cherian, B. S. Kaith, L. Averous, J. Njuguna and E. Nassiopoulos. 2011. Cellulose based bio and nanocomposites: A review. International Journal of Polymer Science 2011:1-35.

Kaushik, M., K. Basu, C. Benoit, C. M. Cirtiu, H. Vali and A. Moores. 2015. Cellulose nanocrystals as chiral inducers: enantioselective catalysis and transmission electron microscopy 3D characterization. Journal of American Chemical Society 137(19):6124-6127.

Keshk, S. M. A. S. 2014. Bacterial cellulose production and its industrial applications. Bioprocessing & Biotechniques 4(2):1-10.

Khalil, H. P. S. A., A. H. Bhat and A. F. Yusra. 2012. Green composites from sustainable cellulose nanofibrils: A review. Carbohydrate Polymers 87(2):963-979.

Khan, A., R. A. Khan, S. Salmieri, C. Le Tien, B. Riedl, J. Bouchard, G. Chauve, V. Tan, M. R. Kamal and M. Lacroix. 2012. Mechanical and barrier properties of nanocrystalline cellulose reinforced chitosan based nanocomposite films. Carbohydrate Polymers 90(4): 1601-1608.

Kim, H. N., A. Jiao, N. S. Hwang, M. S. Kim, D. H. Kang, D.-H. Kim and K.-Y Suh. 2014. Emerging nanotechnology approaches in tissue engineering and regenerative medicine. International Journal of Nanomedicine. 9(S1):1-5.

Kim, J., G. Montero, Y. Habibi, J. P. Hinestroza, J. Genzer, D. S. Argyropoulos and O. J. Rojas. 2009. Dispersion of cellulose crystallites by nonionic surfactants in a hydrophobic polymer matrix. Polymer Engineering & Science 49(10):2054-2061.

Kim, J. and S. Yun. 2006. Discovery of cellulose as a smart material. Macromolecules 39(12):4202-4206.

Kim, J.-W. and R. Deaton. 2013. Molecular self-assembly of multifunctional nanoparticle composites with arbitary shapes and functions: Challenges and strategies. Particle and Particle Systems Characterization 30(2):117-132.

Kim, J.-W. and S. Tung. 2015. Bio-hybrid micro/nanodevices powered by flagellar motor: Challenges and strategies. Frontiers in Bioengineering and Biotechnology 3:100. DOI: 10.3389/fbioe.2015.00100.

Kim, J.-W., E. I. Galanzha and V. P. Zharov. 2014b. In. vivo photoacoustic detection of circulating cells and nanoparticles. In: Frontiers of Nanobiomedical Research-Handbook of Nanobiomedical Research: Fundamentals, Applications and Recent Developments. V. P. Torchilin (ed). World Scientific Publishing Co.

Kim, J.-W., E. I. Galanzha, D. A. Zaharoff, R. J. Griffin and V. P. Zharov. 2013. Nanotheranostics of circulating tumor cells, infections and other pathological features in vivo. Molecular Pharmaceutics 10(3):813-830.

Kim, J.-W., J.-H. Kim and R. Deaton. 2011. DNA-linked nanoparticle building blocks for programmable matter. Angewandte Chemie International Edition 50(39): 9185-9190.

Kim, J.-W., J.-H. Kim and R. Deaton. 2012. Programmable construction of nanostructures: assembly of nanostructures with various components. IEEE Nanotechnology Magazine 6(1):19-23.

Kimura, S. and T. Itoh. 1996. New cellulose synthesizing complexes (terminal complexes) involved in animal cellulose biosynthesis in the tunicate Metandrocarpa uedai. Protoplasma 194(3):151-163.

Klemm, D., B. Heublein, H.-P. Fink and A. Bohn. 2005. Cellulose: Fascinating biopolymer and sustainable raw material. Angewandte Chemie International Edition 44(22):3358- 3393.

Klemm, D., D. Schumann, U. Udhardt and S. Marsch. 2001. Bacterial synthesized cellulose-artificial blood vessels for microsurgery. Progress in Polymer Science 26(9): 1561-1603.

Klemm, D., F. Kramer, S. Moritz, T. Lindstrm, M. Ankerfors, D. Gray and A. Dorris. 2011. Nanocelluloses: A new family of nature-based materials. Angewandte Chemie International Edition 50(24):5438-5466.

Kotagiri, N. and J.-W. Kim. 2014. Stealth nanotubes: Strategies of shielding carbon nanotubes to evade opsonization and improve biodistribution. International Journal of Nanomedicine 9(S1):85-105.

Kumbar, S. G., U. S. Toti, M. Deng, R. James, C. T. Laurencin, A. Aravamudhan and M. Harmon. 2011. Novel mechanically competent polysaccharide scaffolds for bone

tissue engineering. Biomedical Materials 6(6):065005.

Kye, Y.-M., C. Kim and J. Lagerwall. 2015. Multifunctional responsive fibers produced by dual liquid crystal core electrospinning. Journal of Materials Chemistry C 3(34):8979-8985.

Lagerwall, J. P. F., C. Schutz, M. Salajkova, J. H. Noh, J. H. Park, G. Scalia and L. Bergstrom. 2014. Cellulose nanocrystal-based materials: From liquid crystal self-assembly and glass formation to multifunctional thin films. NPG Asia Materials 6(e80):1-12.

Lalia, B. S., Y. A. Samad and R. Hashaikeh. 2013. Nano-crystalline cellulose-reinforced composite mats for lithium-ion batteries: Electrochemical and thermo-mechanical performance Journal of Solid State Electrochemistry 17(3):575-581.

Lam, E., K. B. Male, J. H. Chong, A. C. Leung and J. H. Luong. 2012. Applications of functionalized and nanoparticle-modified nanocrystalline cellulose. Trends in Biotechnology 30(5):283-290.

Lam, E., K. B. Male, J. H. Chong, A. C. Leung and J. H. Luong. 2012. Applications of functionalized and nanoparticle-modified nanocrystalline cellulose. Trends in Biotechnology 30(5):283-290.

Lamaming, J., R. Hashim, C. P. Leh, O. Sulaiman, T. Sugimoto and M. Nasir. 2015. Isolation and characterization of cellulose nanocrystals from parenchyma and vascular bundle of oil palm trunk (*Elaeis guineensis*). Carbohydrate Polymers 134:534-540.

Lavoine, N., I. Desloges, A. Dufresne and J. Bras. 2012. Microfibrillated cellulose-its barrier properties and applications in cellulosic materials: A review. Carbohydrate Polymers 90(1):735-764.

Li, M.-C., Q. Wu, K. Song, Y. Qing and Y. Wu. 2015. Cellulose nanoparticles as modifiers for rheology and fluid loss in bentonite water-based fluids. ACS Applied Materials & Interfaces 7(8):5006-5016.

Li, W., R. Guo, Y. Lan, Y. Zhang, W. Xue and Y. Zhang. 2014. Preparation and properties of cellulose nanocrystals reinforced collagen composite films. Journal of Biomedical Materials Research Part A 102(4):1131-1139.

Li, W., R. Wang and S. Liu. 2011. Nanocrystalline cellulose prepared from soft wood craft pulp via ultrasonicate assisted acid hydrolysis. BioResource 6(4):4271-4281.

Li, W., Y. Lan, R. Guo, Y. Zhang, W. Xue and Y. Zhang. 2014. In vitro and in vivo evaluation of a novel collagen/cellulose nanocrystals scaffold for achieving the sustained release of basic fibroblast growth factor.

Journal of Biomaterials Applications 29(6):882-893.

Li, W.-J., Y. J. Jiang and R. S. Tuan. 2008. Cell-nanofiber-based cartilage tissue engineering using improved cell seeding, growth factor, and bioreactor technologies. Tissue Engineering Part A 14(5):639-648.

Lima, M. M. de S. and R. Borsali. 2004. Rodlike cellulose microcrystals: Structure, properties, and applications. Macromolecular Rapid Communications 25(7):771-787.

Lindman, B., G. Karlström and L. Stigsson. 2010. On the mechanism of dissolution of cellulose. Journal of Molecular Liquids 156(1):76-81.

Lutolf, M. P. and J. A. Hubbell. 2005. Synthetic biomaterials as instructive extracellular microenvironments for morphogenesis in tissue engineering. Nature Biotechnology 23:47-55.

Lynd, L. R., P. J. Weimer, W. H. van Zyl and I. S. Pretorius. 2002. Microbial cellulose utilization: fundamentals and biotechnology. Microbiology and Molecular Biology Reviews 66(3):506-577.

Mallidi, S., G. P. Luke and S. Emelianov. 2011. Photoacoustic imaging in cancer detection, diagnosis, and treatment guidance. Trends in Biotechnology 29(5):213-221.

Marchessault, R. H., F. F. Morehead and N. M. Walter. 1959. Liquid crystal systems from fibrillar polysaccharides. Nature 184:632-633.

Mariano, M., N. E. Kissi and A. Dufresne. 2014. Cellulose nanocrystals and related nanocomposites: Review of some properties and challenges. Journal of Polymer Science, Part B: Polymer Physics 52(2):791-806.

Mastropietro, D. J., R. Nimroozi and H. Omidian. 2013. Rheology in pharmaceutical formulations a perspective. Journal of Developing Drugs 2(2):1-6.

Mihranyan, A. 2011. Cellulose from Cladophorales green algae: From environmental problem to high-tech composite materials. Journal of Applied Polymer Science 119(4):2449-2460.

Mihranyan, A., A. P. Llagostera, R. Karmhag, M. Strømme and R. Ek. 2004. Moisture sorption by cellulose powders of varying crystallinity. International Journal of Pharmaceutics 269(2):433-442.

Miller, A. F. and A. M. Donald. 2003. Imaging of anisotropic cellulose suspensions using environmental scanning electron microscopy. Biomacromolecules 4(3):510-517.

Mohammadkazemi, F., A. Mehrdad and A. Ashori. 2015. Production of bacterial cellulose using different carbon sources and culture media. Carbohydrate Polymers 117:518-523.

Mondragon, G., S. Fernandes, A. Retegi, C. Peña, I. Algar, A. Eceiza and A. Arbelaiz. 2014. A common strategy to extracting cellulose nanoentities from different plants. Industrial Crops and Products 55: 140-148.

Moon, R. J., A. Martini, J. Nairn, J. Simonsen and J. Youngblood. 2011. Cellulose nanomaterials review: Structure, properties and nanocomposites. Chemical Society Reviews 40(7):3941-3994.

Morais, J. P. S., M. de F. Rosa, M. de sá M. de S. Filho, L. D. Nascimento, D. M. do Nascimento and A. R. Cassales. 2013. Extraction and characterization of nanocellulose structures from raw cotton linter. Carbohydrate Polymers 91(1):229-235.

Nair, S. S., J. Y. Zhu, Y. Deng and A. J. Ragauskas. 2014. High performance green barriers based on nanocellulose. Sustainable Chemical Processes 2(23):1-7.

Nascimento, D. M., J. S. Almeida, A. F. Dias, M. C. B. Figueirêdo, J. P. Morais, J. P. A. Feitosa and M. de F. Rosa. 2014. A novel green approach for the preparation of cellulose nanowhiskers from white coir. Carbohydrate Polymers 110:456-463.

Neto, W. P. F., H. A. Silvério, N. O. Dantas and D. Pasquini. 2013. Extraction and characterization of cellulose nanocrystals from agro-industrial residue-soy hulls. Industrial Crops and Products 42:480-488.

Nicolai, E. and R. D. Preston. 1952. cell wall studies in the Chlorophyceae. I. a general survey of submicroscopic structure in filamentous species. Proceedings of the Royal Society B 140(899):244-274.

Ninan, N., M. Muthiah, I.-K. Park, A. Elain, S. Thomas and Y. Grohens. 2013. Pectin/carboxymethyl cellulose/microfibrillated cellulose composite scaffolds for tissue engineering. Carbohydrate Polymers 98:877-885.

Nishiyama, Y., P Langan, M. Wada and V. T. Forsyth. 2010. Looking at hydrogen bonds in cellulose. Acta Crystallographica section D 66(11):1172-1177.

Nogi, M., S. Iwamoto, A. N. Nakagaito and H. Yano. 2009. Optically transparent nanofiber paper. Advanced Materials 21(16):1595-1598.

Nogi, M., S. Iwamoto, A. N. Nakagaito and H. Yano. 2009. Optically transparent nanofiber paper. Advanced Materials 21(16):1595-1598.

Noishiki, Y., Y. Nishiyama, M. Wada, S. Kuga and J. Magoshi. 2002. Mechanical properties of silk fibroin–microcrystalline cellulose composite films. Journal of Applied Polymer Science 86(13):3425-3429.

Normand, M. L., R. Moriana and M. Ek. 2014. Isolation and

characterization of cellulose nanocrystals from spruce bark in a biorefinery perspective. Carbohydrate Polymers 111(2014): 979-987.

Nypelö, T., C. Rodriguez-Abreu, J. Rivas, M. D. Dickey and O. J. Rojas. 2014. Magneto-responsive hybrid materials based on cellulose nanocrystals. Cellulose 21(4):2557-2566.

Olsson, C. and G. Westman. 2013. Direct dissolution of cellulose: background, means and applications. In cellulose-fundamental aspects; Van De Ven, T. G. M., Ed.; InTech: Rijeka, Croatia, pp. 143-178.

Pandey, J. K., S. H. Ahn, C. S. Lee, K. Mohanty and M. Misra. 2010. Recent advances in the application of natural fiber based composites. Macromolecular Materials and Engineering 295(11):975-989.

Park, S. U., B. K. Lee, M. S. Kim, K. K. Park, W. J. Sung, H. Y. Kim, D. G. Han, J. S. Shim, Y. J. Lee, S. H. Kim, I. H. Kim and D. H. Park. 2014. The possibility of microbial cellulose for dressing and scaffold materials. International Wound Journal 11(1):35-43.

Payen, A. 1838. Mémoire sur la composition du tissu propre des plantes et du ligneux. Comptes rendus de l'Académie des Sciences 7:1052-1056.

Peng, B. L., N. Dhar, H. L. Liu and K C. Tam. 2011. Chemistry and applications of nanocrystalline cellulose and its derivatives: A nanotechnology perspective. The Canadian Journal of Chemical Engineering 89(5):1191-1260.

Pérez, R. A., J.-E. Won, J. C. Knowles and H.-W. Kim. 2013. Naturally and synthetic smart composite biomaterials for tissue regeneration. Advanced Drug Delivery Reviews 65(4):471-496.

Persidis, A. 1999. Tissue engineering. Nature Biotechnology 17:508-510.

Place, E. S., N. D. Evans and M. M. Stevens. 2009. Complexity in biomaterials for tissue engineering. Nature Materials 8:457-470.

Podsiadlo, P., L. Sui, Y. Elkasabi, P. Burgardt, J. Lee, A. Miryala, W. Kusumaatmaja, M. R. Carman, M. Shtein, J. Kieffer, J. Lahann and N. A. Kotov. 2007. Layer-by-layer assembled films of cellulose nanowires with antireflective properties. Langmuir 23(15):7901-7906.

Ranby, B. G. 1949. Aqueous colloidal solutions of cellulose micelles. Acta Chemica Scandinavica 3:649-650.

Ranby, B. G. 1951. Fibrous macromolecular systems cellulose and muscle the colloidal properties of cellulose micelles. Discussions of the Faraday Society 11:158-164.

Rodionova, G., M. Lenes, O. Eriksen and O. Gregersen. 2011. Surface chemical modification of microfibrillated

cellulose: improvement of barrier properties for packaging applications. Cellulose 18(1):127-134.

Ross, P., R. Mayer and M. Benziman. 1991. Cellulose biosynthesis and function in bacteria. Microbiological Reviews 55(1):35-58.

Sacui, L. A., R. C. Nieuwendaal, D. J. Burnett, S. J. Stranick, M. Jorfi, C. Weder, E. J. Foster, R. T. Olsson and J. W. Gilman. 2014. Comparison of the properties of cellulose nanocrystals and cellulose nanofibrils isolated from bacteria, tunicate, and wood processed using acid, enzymatic, mechanical, and oxidative methods. ACS Applied Materials & Interfaces 6(9):6127-6138.

Samir, M., F. Alloin and A. Dufresne. 2005. Review of recent research into cellulosic whiskers, their properties and their application in nanocomposite field. Bioma-cromolecules 6(2):612-626.

Santos, R. M., W. P. F. Neto, H. A. Silvério, D. F. Martins, N. O. Dantas and D. Pasquini. 2013. Cellulose nanocrystals from pineapple leaf, a new approach for the reuse of this agro-waste. Industrial Crops and Products 50: 707-714.

Shafiei-Sabet, S., W. Y. Hamad and S. G. Hatzikiriakos. 2012. Rheology of nanocrystalline cellulose aqueous suspensions. Langmuir 28(49):17124-17133.

Sheltami, R. M., I. Abdullah, I. Ahmad, A. Dufresne and H. Kargarzadeh. 2012. Extraction of cellulose nanocrystals from mengkuang leaves (*Pandanus tectorius*). Car-bohydrate Polymers 88(2):772-779.

Shi, Q.-S., J. Feng, W.-R Li, G. Zhou, A.-M. Chen, Y.-S. Ouyang and Y.-B. Chen. 2013. Effect of different conditions on the average degree of polymerization of bacterial cellulose produced by *Gluconacetobacter Intermedius* Bc-41. Cellulose Chemistry and Technology 47(7-8): 503-508.

Shoda, M. and Y. Sugano. 2005. Recent advances in bacterial cellulose production. Biotechnology and Bioprocess Engineering 10(1):1-8.

Shopsowitz, K. E., H. Qi, W. Y. Hamad and M. J. MacLachlan. 2010. Free-standing mesoporous silica films with tunable chiral nematic structures. Nature 468:422-425.

Sickerson, R. F. and J. A. Habrle. 1947. Cellulose inter-crystalline structure. Industrial and Engineering Chemistry 39(11):1507-1512.

Siro, I. and D. Plackett. 2010. Microfibrillated cellulose and new nanocomposite materials: a review. Cellulose 17(3):459-494.

Smith, H. D. 1937. Structure of cellulose. Industrial &

Engineering Chemistry 29(9):1081-1084.

Spence, K.L., R. A. Venditti, O. J. Rojas, J. J. Pawlak and M. A. Hubbe. 2011. Water vapor barrier properties of coated and filled microfibrillated cellulose composite films. Bioresources 6(4):4370-4388.

Staudinger, H. 1920. Über Polymerisation. Berichte der deutschen chemischen Gesellschaft (A and B Series) 53(6):1073-1085.

Sturcova, A., G. R. Davies and S. J. Eichhorn. 2005. Elastic modulus and stress-transfer properties of tunicate cellulose whiskers. Biomacromolecules 6(2):1055-1061.

Sugiyama, J. and T. Okano. 1990. Transformation of Valonia cellulose crystals by an alkaline hydrothermal treatment. Macromolecules 23(12):3198-3200.

Tasset, S., B. Cathala, H. Bizot and I. Capron. 2013. Versatile cellular foams derived from CNC-stabilized pickering emulsions. RSC Advances 4(2):893-898.

Tazi, N., Z. Zhang, Y. Messaddeq, L. Almeida-Lopes, L. M. Zanardi, D. Levinson and M. Rouabhia. 2012. Hyd-roxyapatite bioactivated bacterial cellulose promotes osteoblast growth and the formation of bone nodules. AMB Express 2(1):61-71.

Teixeira, E. M., A. C. Corrêa, A. Manzoli, F. L. Leite, C. R. Oliveira and L. H. C. Mattoso 2010. Cellulose nanofibers from white and naturally colored cotton fibers. Cellulose 17(3):595-606.

Urena-Benavides, E. E., G. Ao., V. A. Davis and C. L. Kitchens. 2011. Rheology and phase behavior of lyotropic cellulose nanocrystal suspensions. Macro-molecules 44(22):8990-8998.

Urena-Benavides, E. E., P. J. Brown and C. L. Kitchens. 2010. Effect of jet stretch and particle load on cellulose nanocrystal-alginate nanocomposite fibers. Langmuir 26(17):14263-14270.

Van de Velde, K. and P. Kiekens. 2001. Thermoplastic pultrusion of natural fibre reinforced composites. Composite structures 54(2-3):355-360.

Wan, Y., C. Gao, M. Han, H. Liang, K. Ren, Y. Wang and H. Luo. 2011. Preparation and characterization of bacterial cellulose/heparin hybrid nanofiber for potential vascular tissue engineering scaffolds. Polymers for Advanced Technologies 22(12):2643-2648.

Wu, Q., Y. Meng, K. Concha, S. Wang, Y. Li, L. Ma and S. Fu. 2013. Influence of temperature and humidity on nano-mechanical properties of cellulose nanocrystal films made from switchgrass and cotton. Industrial Crops and Products 48(2013):28-35.

Yoshinaga, F., J. Tonouchi and K. Watanabe. 1997. Research progress in production of bacterial cellulose by aeration and agitation culture and its application as a new industrial material. Bioscience Biotechnology and Biochemistry 61(2):119-224.

Zhang, Y. P., V. P. Chodavarapu, A. G. Kirk and M. P. Andrews. 2013. Structured color humidity indicator from reversible pitch tuning in self-assembled nano-crystalline cellulose films. Sensors and Actuators B: Chemical 176:692-697.

Zhao, Y. and J. Li. 2014. Excellent chemical and material cellulose from tunicates: diversity in cellulose production yield and chemical and morphological structures from different tunicate species. Cellulose 21(5):3427-3441.

Zhao, Y., Y. Zhang, M. E. Lindström and J. Li. 2015. Tunicate cellulose nanocrystals: Preparation, neat films and nanocomposite films with glucomannans. Carbohydrate Polymers 117:286-296.

Zhao, Y., Y. Zhang, M. E. Lindström and J. Li. 2015. Tunicate cellulose nanocrystals: Preparation, neat films and nanocomposite films with glucomannans. Carbohydrate Polymers 117:286-296.

Zharov, V. P., J.-W. Kim, D. T. Curiel and M. Everts. 2005. Self-assembling nanoclusters in living systems: application of integrated photothermal nanodiagnostics and nanotherapy. Nanomedicine 1:326-345.

Zheng, G., Y. Cui, E. Karabulut, L. Wågberg, H. Zhu and L. Hu. 2013. Nanostructured paper for flexible energy and electronic devices. MRS bulletin 38(4):320-325.

Zhou, C. and Q. Wu. 2012. Recent development in applications of cellulose nanocrystals for advanced polymer-based nanocomposites by novel fabrication strategies. In: nanocrystals-synthesis, characterization and applications. Eds. Sudheer Neralla, pp. 103-120.

Zhou, C., Q. Shi, W. Guo, L. Terrell, A. T. Qureshi, D. J. Hayes and Q. Wu. 2013. Electrospun bio-nanocomposite scaffolds for bone tissue engineering by cellulose nanocrystals reinforcing maleic anhydride grafted PLA. Applied Materials & Interfaces 5(9):3847-3854.

Zhou, J., N. Butchosa, H. S. N. Jayawardena, J.-H. Park, Q. Zhou, M. Yan and O. Ramström. 2015. Synthesis of multifunctional cellulose nanocrystals for lectin recognition and bacterial imaging. Biomacromolecules 16:1426-1432.

Zhou, Q., H. Brumer and T. T. Teeri. 2009. Self-organization of cellulose nanocrystals adsorbed with xyloglucan oligosaccharide-poly(ethylene glycol)-polystyrene triblock copolymer. Macromolecules 42(15):5430-5432.

Zugenmaier, P. 2008. History of Cellulose Research. In: *Crystalline Cellulose and Cellulose Derivatives*, pp. 7-51. Berlin: Springer Verlag.