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This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims for obviousness. We have jurisdiction under 35 U.S.C. § 6(b). We REVERSE and enter a new ground of rejection.

NATURE OF THE INVENTION

The present disclosure provides multifunctional cytoprotective materials applied to coat living cells or aggregates of cells such as, but not limited to, pancreatic islets. The coating utilizes hydrogen-bonded interactions of a natural polyphenol (tannic acid) with poly(N-vinylpyrrolidone) deposited on the cell aggregate surface via non-ionic layer-by-layer assembly. The coating is conformal over the surface of such as mammalian islets. The coated islets maintain their viability and cell functionality for at least 96 hours in vitro. The coating demon-
strates immunomodulatory cytoprotective properties suppressing proinflammatory cytokine synthesis in stimulated bone marrow-derived macrophages and diabetogenic B DC-2.5 T cells.

Spec. 6–7. In particular, pancreatic “[i]slet encapsulation can provide a means of culturing and delivering islets for transplantation purposes (Beck et al., (2007) Tissue Eng. 13: 589-599). This technique allows for creation of a semi-permeable environment around a group of islets to provide an immune-protection and to allow mass and oxygen transfer.” Spec. 2.

STATEMENT OF CASE

The following claim is representative.

1. A biocompatible coating disposed on a cell or aggregate of cells, the coating comprising a first polymer layer attached to the membrane or membranes of a cell or aggregate of cells by hydrogen-bonding and encapsulating said cell or cell aggregate, wherein said first polymer layer comprises poly(N-vinylpyrrolidone) (PVPON), wherein said PVPON has a molecular weight of about 1,300,000 daltons, and a second polymer layer disposed on the first polymer layer and attached thereto by hydrogen-bonding, wherein the second polymer layer is a polyphenolic tannin layer, and wherein the cell, or aggregate of cells, is isolated from an animal or human tissue or is a cultured cell or an aggregate of cultured cells.

Cited References

Sukhishvili US 2005/0163714 A1 July 28, 2005

Grounds of Rejection  
Claims 1–3, 6–9, 12–15, and 19² are rejected under pre-AIA 35 U.S.C. §103(a) as being unpatentable over Sukhishvili, Kozlovskaya in view of Kizilel and Kothwala, as evidenced by Stendahl. Final Act. 3.  

We summarily reverse this rejection and enter a new ground of rejection under 35 U.S.C. §103(a).  

¹ Although Kozlovskaya is a named inventor in the present application, Appellants do not dispute that this reference qualifies as prior art under pre-AIA 35 U.S.C. §102(b).  
² Claims 7 and 19 were cancelled by Appellants in an Amendment filed June 7, 2017. The Examiner’s Advisory Action dated June 22, 2017 indicated that the Amendment filed June 7, 2017 “will be entered.” Therefore, claims 1–3, 6, 8–9, and 12–15 are pending on appeal.
New Ground of Rejection

Claims 1–3, 6, 8–9, and 12–15 are rejected under pre-AIA 35 U.S.C. §103(a) as being unpatentable over Kozlovskaya in view of Kizilel.

FINDINGS OF FACT

The following facts are highlighted.

1. Kozlovskaya teaches a capsule comprising PVPON/TA (poly-N-vinylpyrrolidone 1300000/tannic acid) LbL (layer-by-layer) multilayers, wherein the second polymer layer (the outermost polymer layer) is a polyphenolic tannin layer (p. 3599, p.3601 col right – para 3, p. 3606 col left – para 3). Alexa Fluor 488 dye (detectable moiety) is added to the capsule (at least one polymer layer further comprises a functional moiety attached thereto) (p.3607 col left – para 2).

2. Kozlovskaya states that

Interest to [sic] tannic acid (TA) as a molecule with the ability to multiple hydrogen bonding due to the presence of numerous terminal hydroxyl groups has been spiked relatively recently due to its high biological activity including antioxidant, antimicrobial, anticarcinogenic, antimitagenic and antibacterial properties. The anticarcinogenic and antimitagenic potentials of polyphenols are related to their antioxidative property in protecting cellular components from oxidative damage. It is due to unique functional structure of tannic acid, which possesses maximum number of hydroxyl groups compared to other derivatives of tannins, the antioxidant properties of TA are revealed. As reported, polyphenols possess high ability to reduce free-radicals and inhibit radical-induced oxidation of adjacent molecules.

P. 3597, col 1.
3. Kozlovskaya teaches a biocompatible coating where multiple layers are formed on various cores through a stepwise template adsorption of proper species—biological molecules, polymers, organic polymers, and nanoparticles. P. 3596, col. 1.

4. The Kozlovskaya encapsulation technology for therapeutic delivery uses hydrogen-bonded Layer-by-layer (LbL) techniques. P. 3596, col 2. Figure 2 of Kozlovskaya discloses 3 LbL layer capsules (PEI/PVPON/TA). P. 3598, col. 2.

5. Kozlovskaya discloses that, “the permeability of the LbL containers can be controlled by changing pH providing an opportunity for loading and release of a functional cargo under mild conditions.” Abstract. Kozlovskaya further discloses that the magnitude of negative charges associated with increasing pH is lower when PVPON with higher molecular weight was used for the capsule shell fabrication. P. 3602.

6. Kozlovskaya discloses that charge screening differences are “probably reflective of better negative charge screening by longer PVPON chains and consistent with the thicker TA/PVPON-1300 [3] shells with the same number of deposited layers (Table 1)” Id. PVPON/TA capsules showed no capsule dissolution, and no distinctive change in capsule diameter. P. 3601, col. 2.

7. Kozlovskaya tested various capsule compositions under “biologically relevant conditions.” P. 3600, col. 2. PVPON has been investigated as a potential pH-stable material for sustain release formulations. P. 3597.

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3 PVPON 1300000 Da.
8. Kozlovskaya discloses that

The observed high capability of TA/PVPON films to withstand an internal ionization within the multilayer can be explained by the ability of TA to form intra-molecular hydrogen bonds. Such stabilizing effect can be enhanced with the increase of a number of participating phenolic units.

P. 3603, col. 1.

9. Kozlovskaya discloses that, “Hydrogen-bonded (TA/non-ionic polymer) coatings can be fanned either through deposition on PEI-treated silica particles (IA) starting from TA or through direct deposition of the (nonionic polymer/TA) multilayer starting from a neutral polymer. P. 3598, Fig. 2 description.

10. Kozlovskaya concludes that

These properties of the reported shells can find a potential use for the fabrication of responsive ultra thin yet robust microcapsules for biochemical sensing and detection as well as laser- or chemically-induced cargo release for biotechnology applications.

P. 3606, col. 1.

11. Kizilel teaches encapsulation of pancreatic islets for transplantation of islets, within a multilayered LbL film for enhanced insulin secretion (Title), wherein mouse pancreatic islets are isolated from a pancreatic tissue (p. 2219 col left – para 4), cultured (p. 2219 col right – para 2), coated via layer-by-layer assembly technique. The capsules and are capable of secreting more insulin (produce a molecule modulating the physiology of an animal) (Abstract).

12. Kizilel suggests that, blood-mediated inflammatory reactions are likely cause of both the loss of transplanted
islet tissue and the intraportal thrombosis associated with clinical islet transplantation. P. 2218, col. 1.


PRINCIPLES OF LAW

“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

*New Ground - Obviousness Rejection*

Claims 1–3, 6, 8–9, and 12–15 are rejected under pre-AIA 35 U.S.C. §103(a) as being unpatentable over Kozlovskaya in view of Kizilel.

Independent claim 1 recites a biocompatible coating disposed on a layer of isolated or cultured cell(s), wherein the coating is comprised of a first polymer layer of PVPON with a molecular weight of 1,300,000 daltons attached to the cell membrane(s) by hydrogen bonding, and a second polymer layer of polyphenolic tannin attached to the first polymer layer also by hydrogen bonding. Kozlovskaya teaches a biocompatible coating where multiple layers are formed on various cores through a stepwise template adsorption of proper species—biological molecules, polymers, organic polymers, and nanoparticles. P. 3596, col. 1.
Kozlovskaya discloses that, “the permeability of the LbL containers can be controlled by changing pH providing an opportunity for loading and release of a functional cargo under mild conditions.”

Abstract. Kozlovskaya further discloses that the magnitude of negative charges associated with increasing pH is lower when PVPON with a higher molecular weight was used for the capsule shell fabrication. P. 3602. In particular, Kozlovskaya teaches that charge screening differences are “probably reflective of better negative charge screening by longer PVPON chains and consistent with the thicker TA/PVPON-1300 \(^4\) shells with the same number of deposited layers (Table 1).” Id. Kozlovskaya tested various capsule compositions under “biologically relevant conditions.” P. 3600, col. 2. PVPON/TA capsules showed no capsule dissolution, and no distinctive change in capsule diameter. P. 3601, col. 2. PVPON has been investigated as a potential pH-stable material for sustain release formulations. P. 3597. Kozlovskaya discloses that

The observed high capability of TA/PVPON films to withstand an internal ionization within the multilayer can be explained by the ability of TA to form intra-molecular hydrogen bonds. Such stabilizing effect can be enhanced with the increase of a number of participating phenolic units.

P. 3603, col. 1. Kozlovskaya concludes that

These properties of the reported shells can find a potential use for the fabrication of responsive ultra thin yet robust microcapsules for biochemical sensing and detection as well as

\(^4\) PVPON 1300000 Da.
laser- or chemically-induced cargo release for biotechnology applications.

P. 3606, col. 1. Kozlovskaya discloses that, “Hydrogen-bonded (TA/non-ionic polymer) coatings can be formed either through deposition on PEI-treated silica particles (IA) starting from TA or through direct deposition of the (nonionic polymer/TA) multilayer starting from a neutral polymer.” FF 9. While Kozlovskaya teaches the encapsulation technology can be used with biological materials and organic polymers, Kozlovskaya does not specifically disclose that the encapsulation technology can be used with cells or cell aggregates. Kizilel discloses that it was well known in the art at the time of the invention to encapsulate pancreatic islet cells using LbL technology (for example with a polyethylene glycol polymer) for pancreatic islet cell transplantation. P. 2217-2218. Kizilel discloses that those of skill in the art look for islet cell transplant structures which are stable under physiological conditions. P. 2221, col. 1.

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to substitute the LbL PVPON/TA 1300 capsule technology of Kozlovskaya for the LbL encapsulation technology of Kizilel for pancreatic islet cell transplantation, because the encapsulation technology of Kozlovskaya exhibits greater stability under physiologic pH conditions and Kizilel indicates that stability under physiologic conditions is a desired property of capsules for delivery of islet cells for transplantation. It would have been further obvious to substitute the LbL technology of Kozlovskaya for that of Kizilel for the benefits associated with the use of
tannic acid for its high biological activity including antioxidant, antimicrobial, anticarcinogenic, antimutagenic and antibacterial properties, which would have been understood by those of ordinary skill in the art to be particularly desirable when cells are being used. Kizilel suggests that LbL coatings of islet cells provides potential for immunoisolation of pancreatic transplant cells. Abstract. Therefore, one of ordinary skill in the art would have looked to stable, biocompatible, LbL coating/encapsulation technologies, such as that of Kozlovskaya, to provide improved immunoisolation to pancreatic cell transplants.

With respect to claims 2–3, Kozlovskaya discloses multilayer capsules as required. P. 3597, col. 2. The term “multiple” means “consisting of, or including more than one,” which encompasses as many as 3 or more coating/capsule layers. The Kozlovskaya coating/encapsulation technology for therapeutic delivery uses hydrogen-bonded Layer-by-layer (LbL) techniques. P. 3596, col 2. In addition, Figure 2 of Kozlovskaya discloses 3 LbL layer capsules (PEI/PVPON/TA). P. 3598, col. 2. With respect to claims 6, 8, 9, and 12–15, Kozlovskaya discloses functional moieties on the capsules, such as fluorescent probe. P. 3603, col. 1. We, therefore, determine that these dependent claims are also obvious in view of the foregoing cited prior art teachings and rationale.

DISCUSSION

We enter a new ground of rejection in the application, but for the sake of compact prosecution, we entertain Appellants’ pending arguments of record that address the Kozlovskaya and Kizilel references.

5 https://www.merriam-webster.com/dictionary/multiple
Appellants contend that the
Examiner failed … to address that the capsules taught by *Kozlovskaya* were formed layer-by-layer on silicon cores that are subsequently removed under acid (pH 2) conditions. The acid treatment results in hollow capsules that are not shown capable of receiving cells or aggregates of cell (pancreatic islets).

Appellants assert that the addition of the tannic acid layer as taught by *Kozlovskaya* was conducted at a pH of either 5.0 or 2.0 (see *Kozlovskaya* at page 3606, second col. last paragraph), [which are] values that one of skill in the art would readily recognize is far below a physiological pH and will, therefore, have likely detrimental consequences for the viability or physiology of the cell or cell aggregate being coated. Therefore, it cannot be construed that there is a reasonable expectation of success contrary to the assertion of the Office Action. In short, one skilled in the art would not use the teachings of *Kozlovskaya* and apply them to the other cited references, alone or in combination, to arrive at the coated functioning pancreatic cells as argued by Examiner.


Appellants further contend that

*Kozlovskaya* does not mention biocompatibility and its teachings are contrary to the alleged reliance on *Kozlovskaya* to demonstrate that tannic acid-based multilayer assemblies are used as biocompatible coatings. Rather, as stated by the Non-Final Office Action, tannic acid (a polyphenol) has a high biological activity that includes antioxidant, antimicrobial, anticarcinogenic, antimutagenic and antibacterial properties, none of which should be construed as related to, or indicating, biocompatibility. Accordingly, Appellants maintain that the use of tannic acid in the constructs of the present application that are used for the maintenance of living cells is not suggested or taught by *Kozlovskaya*.

Appellant's reply on the Declaration under 35 U.S.C. § 1.132 of Eugenia Kharlampieva Ph.D (hereinafter, Declaration), as evidence that the state of knowledge at the time of the invention was that tannic acid is cytotoxic, and that tannic acid would have been expected to leach from a PVPON LbL. App. Br. 8. Dr. Kharlampieva states that only the compositions of the present application incorporating poly-N-vinylpyrrolidone with a molecular weight of about 1,300,000 allow tannic acid to be incorporated into the LbL without adverse effects on the encapsulated cells. Id.

We are not persuaded by Appellant's arguments. Kozlovskaya expressly discloses that “tannic acid exhibits antioxidative property that protects cellular components from oxidative damage (p.3597 col left para 4).” Thus, we find one of ordinary skill in the art would have understood that the coating/capsules of Kozlovskaya would be beneficial in the cellular environment to prevent oxidative damage to cells. In addition, Kozlovskaya does teach PVPON-1300 (MW= 1300000 Da)/tannic acid multilayer assemblies (Table 1), the same structure that is claimed. FF 1. Because the compositions of Kozlovskaya incorporating PVPON with a molecular weight of about 1,300,000 allows tannic acid to be incorporated into the LbL without adverse effects on the encapsulated cells, we find that the PVPON-1300 (MW= 1300000 Da)/tannic acid multilayer assemblies of Kozlovskaya are necessarily biocompatible.

The Declaration does not fully address the teachings of Kozlovskaya with respect to microcapsule therapeutic delivery of biological molecules and the biocompatibility of the microcapsules. P. 3596. The coating/capsules of Kozlovskaya are essentially the same as those claimed,
and therefore, would inherently possess the same chemical characteristics and biocompatibility properties. “From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing.” *In re Papesch*, 315 F.2d 381, 391 (CCPA 1963).

Where . . . the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product…. Whether the rejection is based on “inherency” under 35 U.S.C. § 102, on “prima facie obviousness” under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO’s inability to manufacture products or to obtain and compare prior art products.

*In re Best*, 562 F.2d 1252, 1255 (CCPA 1977) (emphasis added.) Appellants have not shown that the prior art capsules of Kozlovskaya do not necessarily or inherently possess the biocompatibility characteristics of the claimed coating/capsules.

Appellants argue that Kozlovskaya does not mention biocompatibility of the capsules and its teachings are contrary to the alleged reliance on Kozlovskaya to demonstrate that tannic acid-based multilayer assemblies are used as biocompatible coatings. App. Br. 8. We are not persuaded. Kozlovskaya discloses that microcapsules generally, including TA/PVPON-1300 microcapsules disclosed therein,6 “[c]an find a potential use for the fabrication of responsive ultra thin yet robust microcapsules for biochemical sensing and detection as well as laser- or chemically-induced cargo release

6 Tannic acid polyvinyl pyrrolidone capsule, molecular weight 1,300,000.
for biotechnology applications.” P. 3606, col. 1. The Kozlovskaya capsules are made from functional polymers expressly identified as “biocompatible” and capable of “protecting cellular components from oxidative damage.” P. 3597, col. 1. Kozlovskaya further teaches that it was well known in the art that layer-by-layer assembly of micro- and nano shells have been used with cores of biological molecules. P. 3596, col. 1. Thus, Kozlovskaya suggests that its microcapsules are appropriate for use with biological molecules.

Nor do we find that the Declaration provides a showing of unexpected results for the TA/PVPON 1300000 microcapsules with islet pancreatic cells, in view of the particular disclosures of Kozlovskaya. Kozlovskaya teaches that, “it is evident that the magnitude of such increase [in negative charges] is lower when PVPON with higher molecular weight was used for the capsule shell fabrication.” P. 3602 and Fig. 10. Thus, Kozlovskaya would have suggested that one of ordinary skill in the art should use higher molecular weight PVPON, such as 1300000 PVPON, which has favorable pH stability.

Appellants’ Declaration, Exhibit N (Lybaert), also supports a prima facie case of obviousness. Lybaert discloses that

These data point out the superior performance of TA and PVP, compared to polyelectrolytes to encapsulate cells in a polymeric multilayer coating while maintaining membrane integrity as much as possible and affecting cell viability as little as possible.

P. 7142, col. 2. Lybaert did teach a dramatic reduction in cell viability when only two bilayers were used. Pl. 7143-7144. However, Lybaert also teaches greater cell viability when the layered capsule begins with a PVP layer vs. a TA layer, and when multiple layers are used. P. 7144, col. 1; p. 7146, col. 1.
Appellants assert that Kizlel merely teaches only the placing of a coating on cells. App. Br. 9.

Kizlel teaches a coating formed by the covalent attachment of biotin-PEG-NHS monomers to \(-\text{NH}_2\) groups on the surfaces of the cells (Kizlel at Fig. 1). Streptavidin then binds to the biotin followed by biotin-PEG-GLP1 monomers binding to the streptavidin.

Accordingly, the interaction between the first layer (as defined by Kizlel) and the cells is by covalent bonding of monomers and is markedly different from the hydrogen bonding of PVPON polymers as taught and claimed in the present application. App. Br. 9, without emphasis.

Kizlel is relied upon to demonstrate that an isolated pancreatic islet dissected from a pancreas can be encapsulated in a polymer, such as polyethylene glycol LbL, to enhance insulin secretion. Kizilel is not relied on for the teaching of a hydrogen bonded LbL capsule, but instead for its teaching that LbL capsule technology generally is appropriate for use in delivery of pancreatic islet cells for transplantation and cargo release for biotechnology applications. We find nothing in Kizilel to suggest that only polymers that form covalent bonds with cells are appropriate for LbL capsule technology used in biotechnology applications. As discussed above, Kozlovskaya teaches a hydrogen bonded LbL encapsulation technology for biomaterials. Furthermore, Kizlel teaches that there is a need to develop islet encapsulation strategies to minimize transplant volume and immunoisolate transplant cells (Abstract). Thus, one of ordinary skill in the art would have looked to other biocompatible encapsulation polymers known in the art, such as those of Kozlovskaya, with an expectation of success because these polymer encapsulation systems are indicated to be
appropriate for biological materials, including cells, and are stable in the physiological environment.

Appellants argue that the capsules taught by Kozlovskaya were formed layer-by-layer on silicon cores that are subsequently removed under acid (pH 2) conditions. The acid treatment results in hollow capsules that are not shown capable of receiving cells or aggregates of cell (pancreatic islets).

We are not persuaded that the particular methodology described in the experimental section of Kozlovskaya forecloses obviousness. According to the experimental procedures of Kozlovskaya, the capsules were formed over silica cores, which were later removed at low pH, 2. P. 3606, col. 1. The capsules were then loaded with gold after exposure to borate buffers to activate the tannic acid, and centrifugation. P. 3606, cols. 1 and 2. Thus, the acid treatment would have occurred before the capsules are loaded with their cargo, e.g. cells. Furthermore, Kozlovskaya generally teaches a biocompatible coating where multiple layers are formed on various cores through a stepwise template adsorption of proper species—biological molecules, polymers, organic polymers, and nanoparticles. P. 3596, col. 1. Thus, we find Kozlovskaya teaches biocompatible encapsulation technology that can be used to coat cells in the same manner as Kizilel’s disclosure of pancreatic islet cell transplant coatings.

CONCLUSION OF LAW

The Examiner’s obviousness rejection is reversed. However, a new ground of rejection of claims 1–3, 6, 8–9, and 12–15 is entered into the application.
TIME PERIOD FOR RESPONSE

This decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b). 37 C.F.R. § 41.50(b) provides that “[a] new ground of rejection ... shall not be considered final for judicial review.”

37 C.F.R. § 41.50(b) also provides that the Appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

(1) Reopen prosecution. Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the proceeding will be remanded to the examiner. . . .

(2) Request rehearing. Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

REVERSED AND NEW GROUND UNDER 37 C.F.R. § 41.50(b)