UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/897,030	02/14/2018	Stephen James Russell	07039-1267002	3866

26191 7590 08/28/2020

FISH & RICHARDSON P.C. (TC)
PO BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER
GALISTEO GONZALE, ANTONIO

ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
08/28/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

UNITED STATES PATENT AND TRADEMARK OFFICE

_____

BEFORE THE PATENT TRIAL AND APPEAL BOARD

_____

Ex parte STEPHEN JAMES RUSSELL

_____

Appeal 2020-000970
Application[1] 15/897,030
Technology Center 1600

_____

Before ULRIKE W. JENKS, AMEE A. SHAH, and
RACHEL H. TOWNSEND, *Administrative Patent Judges*.

TOWNSEND, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to a method for treating diabetes, which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

STATEMENT OF THE CASE

"Insulin replacement therapy is the mainstay of treatment for all patients with type I diabetes and for many patients with type II diabetes." (Spec. 1) "Inadequate insulin leads to[, among other things,] hyperglycemia

---

[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party in interest as Mayo Foundation for Medical Education and Research. (Appeal Br. 2.)

. . . . At the other extreme, excess insulin causes life-threatening hypoglycemia." (*Id.*) Appellant's invention is directed at an insulin gene therapy approach "ensuring that (a) an adequate quantity of insulin is produced and (b) insulin overproduction and fatal hypoglycemia are reduced or avoided." (*Id.* at 2.)

Claims 1–11 are on appeal. Claim 1 is representative and reads as follows:

> 1. A method for treating diabetes, wherein said method comprises administering, to a mammal with diabetes, a vector comprising a nucleic acid construct comprising a nucleic acid encoding an insulin polypeptide and a nucleic acid encoding an inducible death switch polypeptide.

(Appeal Br. 16.)

The prior art relied upon by the Examiner is:

Name	Reference	Date
Clarke	US 2007/0066552 A1	Mar. 22, 2007
Brenner	US 2011/0286980 A1	Nov. 24, 2011
Kay	US 2013/0210897 A1	Aug. 15, 2013
M. Yanagita et al., *Processing of mutated proinsulin with tetrabasic cleavage sites to bioactive insulin in the non-endocrine ceil line, COS-7*, 311(1) FEBS 55–59 (1992)		

The following grounds of rejection by the Examiner are before us on review:

Claims 1–7, 9, and 10 under 35 U.S.C. § 103(a) as unpatentable over Clarke and Brenner.

Claims 1–10 under 35 U.S.C. § 103(a) as unpatentable over Clarke, Brenner, and Yanagita.

Claims 1–7 and 9–11 under 35 U.S.C. § 103(a) as unpatentable over Clarke, Brenner, and Kay.

DISCUSSION

The Examiner finds that Clarke teaches a polycistronic construct "comprising a therapeutic gene and a proapoptotic gene and describe[s] a method for treating diabetes (condition to be treated or prevented may be diabetes; [paragraph [0470])." (Final Action 3.) The Examiner finds that Clarke teaches the "therapeutic nucleic acid may encode a therapeutic protein, such as a proapoptotic protein (meaning a protein that promotes apoptosis) and a cytokine; paragraph [0028]; examples of such cytokines are insulin and proinsulin; paragraph [0107]." (*Id.*) The Examiner concludes that the proapoptotic protein meets the "inducible death switch polypeptide" required by the claimed vector used in the claimed treatment method. (*Id.*; *see also* Ans. 6 ("In the case of proapoptotic proteins, caspase-3 is recited as an exemplary proapoptotic protein. . . . It was known in the art at the time of filing that caspase-3 could be induced to promote apoptosis by the administration of butyrate. Therefore, caspase-3, as defined by the specification, is an inducible death switch polypeptide.").)

The Examiner further finds that Clarke teaches that the nucleic acid construct in the expression cassette carried in the viral vector to be administered

> comprises an IRES located between said nucleic acid encoding said insulin polypeptide and said nucleic acid encoding an inducible death switch polypeptide (the use of internal ribosome entry sites (IRES) elements are used to create multigene, or polycistronic, messages. By virtue of the IRES

> element, each open reading frame is accessible to ribosomes for efficient translation . . . paragraph [0218].

(*Id.* at 3–4.)

The Examiner finds that "Brenner is directed to polycistronic constructs comprising a therapeutic gene and a proapoptotic gene" where the proapoptotic gene is "an iCasp9" which is an inducible death switch polypeptide whose inducing agents include AP1901 and AP20187. (*Id.* at 4–5.) The Examiner finds that Brenner teaches that "cells expressing an inducible caspase 9 protein may be selectively killed if the patient experiences dangerous side effects (abstract)." (*Id.* at 5.)

The Examiner determines that "it would have been [obvious] to a person of ordinary skill in the art at the time of filing to have the method described by Clarke et al. and include iCasp9 protein as the proapoptotic peptide as described by Brenner." (*Id.*) The Examiner reasons that "it would have been obvious if a patient experiences hypoglycemia from overexpression of insulin from the vector, administering the inducing agent will kill cells expressing the vector, reducing said hypoglycemia." (*Id.*) The Examiner determines that the "skilled artisan would have had a reasonable expectation that a construct comprising the insulin gene of Clarke et al. and the iCasp9 gene of Brenner would express insulin in a cell, and upon administration of the inducing agent, it would express iCasp9, thereby killing said cell and controlling insulin production." (*Id.*)

We disagree with the Examiner's factual findings regarding Clarke and conclusion of obviousness.

I. Clarke

In particular, as Appellant notes, Clarke does not describe the combination of a nucleic acid encoding insulin polypeptide and nucleic acid

encoding an inducible death switch polypeptide, much less with an IRES to provide for a polycistronic message. (Appeal Br. 6–8.) And we conclude that such a construct is not reasonably suggested from the disclosure of Clarke.

A. Clarke's disclosure concerning Insulin Therapy

First, with respect to treating diabetes, Clarke teaches "administering a modulator of human ACC" that may "precede, follow, or be concurrent with other therapies for diabetes, such as an oral hypoglycemic acid or insulin therapy." (Clarke ¶ 470.) Thus, Clarke teaches insulin therapy to be something different from a modulator of human ACC. We do not find in Clarke any definition or other indication of what a modulator of human ACC is. Even, if one were to assume that it is a therapeutic nucleic acid formulation suggested by Clarke, it is not clear why it would be reasonable to conclude from Clarke that a nucleic acid encoding insulin would be part of that formulation to treat diabetes which would be additional to "insulin therapy." (*Id.*)

B. Clarke's disclosure concerning insulin and "formulations of nucleic acids" for use in "the diagnosis, treatment, and prevention of disease"

Second, regarding the claimed formulation to be administered, the only other mention of "insulin" in Clarke is in an extensive list of what are generally known to be cytokines. (*Id.* ¶ 107.) Clarke indicates that "[i]n some embodiments of the pharmaceutical compositions set forth herein the [therapeutic] nucleic acid encodes a cytokine." (*Id.* ¶ 106.) Then Clarke provides a definition of cytokine as follows:

> The term "cytokine" is a generic term for proteins released by one cell population which act on another cell as intercellular mediators.

(*Id.*) Clarke next indicates: "Examples of such cytokines are lymphokines, monokines, growth factors and traditional polypeptide hormones." (*Id.* ¶ 107.) And then Clarke provides a list of specific compounds that are growth hormones that are considered cytokines, which list includes insulin. (*Id.*)

Even if one were to conclude that the foregoing listing of insulin as a cytokine is a suggestion by Clarke to make a composition of a nucleic acid encoding insulin to treat diabetes, we do not find a further reasonable suggestion in Clarke that such composition should be combined with a proapoptotic nucleic acid sequence. That is because Clarke's "novel formulations" teachings are focused on compositions that "facilitate more efficient delivery and targeting of a nucleic acid of interest to target cells in a subject." (Clarke ¶ 18, *see also id.* ¶ 16 (noting there is a need for: "Compositions of therapeutic nucleic acids which allow for prolonged contact of the nucleic acid with the appropriate target cells would improve therapeutic efficacy of the formulation. Methods of delivery of a reporter gene to diseased cells of a subject might provide for more improved ability to target and detect diseased cells.").) The therapeutic nucleic acid itself is not the focus. Indeed, Clarke explains that the compositions "involve nucleic acids that are known or suspected to be of benefit in the diagnosis, treatment, or prevention of a disease or health-related condition in a subject." (*Id.* ¶ 71.) As to the therapeutic protein, Clarke explains that "[t]he therapeutic nucleic acid may encode a therapeutic protein, such as a tumor suppressor, a proapoptotic protein (meaning a protein that promotes apoptosis), a cytokine, a growth factor, a hormone, a tumor antigen, *or* an enzyme." (*Id.* ¶ 28 (emphasis added).)

Clarke does teach that nucleic acids that encode proapoptotic proteins can be a therapeutic nucleic acid. (*Id.* ¶¶ 97, 102.) However, there is no specific mention of combining a proapoptotic protein with a cytokine, much less with insulin specifically. Rather, Clarke separately lists nucleic acids that encode tumor suppressors and proapoptotic proteins as therapeutic proteins (*id.* ¶¶ 97–104) separately from cytokines (*id.* ¶¶ 105–110), as well as separately listing nucleic acids encoding enzymes (*id.* ¶¶ 111–114), nucleic acids encoding hormones (*id.* ¶¶ 115–119), nucleic acids encoding antigens (*id.* ¶¶ 120–149), and nucleic acids encoding antibodies (*id.* ¶¶ 150–152) as possible therapeutic nucleic acids. And we conclude that such disclosure does not suggest combining a proapoptotic protein with a cytokine.

C. Clarke's disclosure concerning a polycistronic construct

Third, with respect to a polycistronic construct, Clarke simply mentions in passing in the lengthy discussion of elements of the genetic constructs containing a therapeutic nucleic acid, i.e., an expression cassette (*id.* ¶ 199), that an IRES is "used to create multigene, or polycistronic messages" (*id.* ¶ 218). In light of the foregoing, we do not agree with the Examiner that Clarke reasonably suggests a polycistronic vector comprising insulin and a proapoptotic protein, much less where that proapoptotic protein is an inducible death switch polypeptide (Ans. 6). (*See* Reply Br. 2.)

II. The Combination of Clarke and Brenner

Furthermore, we do not find Brenner in combination with Clarke renders a composition including insulin and an inducible death switch polypeptide obvious. That is because Brenner is directed to modifying a T cell with inducible death switch polypeptide and administering such a

modified T cell to prevent graft versus host disease. (*See, e.g.*, Brenner ¶¶ 3, 7.) Although, Brenner, like Clarke, has a generic discussion about using IRES elements for polycistronic messages (*id.* ¶ 181), it does not suggest combining a nucleic acid encoding a therapeutic protein in combination with a nucleic acid encoding a proapoptotic polypeptide. On this record, that teaching is only provided by Appellant's Specification.

For the foregoing reasons, therefore, we do not affirm the Examiner's rejection of claims 1–7, 9, and 10 as being obvious from Clarke and Brenner.

The Examiner's additional rejections add references that do not cure the foregoing defects. Consequently, we also do not affirm the Examiner's rejection of claims 1–10 as obvious from Clarke, Brenner, and Yanagita or of claims 1–7 and 9–11 as obvious from Clarke, Brenner, and Kay.

DECISION SUMMARY

In summary:

Claims Rejected	**35 U.S.C. §**	**Reference(s)/Basis**	**Affirmed**	**Reversed**
1–7, 9, 10	103	Clarke, Brenner		1–7, 9, 10
1–10		Clarke, Brenner, Yanagita		1–10
1–7, 9–11		Clarke, Brenner, Kay		1–7, 9–11
Overall Outcome				1–11

REVERSED