PATENT ASSIGNMENT

Electronic Version v1.1
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SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
Dennis G. Cvitkovitch	04/01/2000
Peter Chun Yu Lau	04/01/2000
Yung-Hua Li	04/01/2000

RECEIVING PARTY DATA

Name:	The Governing Council of the University of Toronto
Street Address:	27 King's College Circle
Internal Address:	Simcoe Hall, Room 133S
City:	Toronto
State/Country:	ONTARIO
Postal Code:	M5S 1A1

PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	11005636

CH $40.00 11005636

CORRESPONDENCE DATA

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ATTORNEY DOCKET NUMBER:	2224-01302
NAME OF SUBMITTER:	Carol G. Mintz

Total Attachments: 14
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University of Toronto
OFFICE OF THE VICE-PRESIDENT, RESEARCH AND ASSOCIATE PROVOST

ASSIGNMENT OF RIGHTS TO THE UNIVERSITY OF TORONTO BY THE INVENTOR

In consideration of the terms and mutual covenants hereinafter contained and other good and valuable consideration in the sum of Two Dollars ($2.00) of lawful money of Canada paid by each of the parties to the other, the receipt and sufficiency of which are hereby acknowledged **Dennis G. Cvitkovitch, Peter Chun Yu Lau and Yung-Hua Li**, and their heirs, executors, administrators and assigns (collectively the "**Assignor**") and **The Governing Council of the University of Toronto**, its successors and assigns (collectively the "**Assignee**") covenant and agree as follows:

1. As used in this Assignment, "Net Revenues" shall mean the royalty, licensing and other revenue received by the Assignee from all rights held by the Assignee in the invention entitled "**Inhibitors of Peptide-Mediated Virulence of Mutans Streptococci**" as described in Appendix A annexed hereto (the "Invention") less legal and other fees that the Assignee incurs directly in the process of establishing and maintaining the legal protection of those rights.

2. The Assignor hereby assigns to the Assignee all right, title and interest, whatever the same may be (but without any representation or warranty as to the nature, extent or validity thereof) which the Assignor now has or may in the future have in the Invention including without limitation the right to apply for patents in Canada, the United States of America and any other country, the right to receive any letters patent that may be issued from any such applications and the right to sell, license or assign the Invention or the rights thereto.

3. In consideration of the rights granted the Assignee pursuant to this Assignment, the Assignee agrees to pay the Assignor 75% Net Revenues.

4. If an arrangement for commercialization of the Invention is made which provides consideration to the Assignee other than cash, the parties will share the proceeds of such non-cash consideration in the same proportion as provided in paragraph 3.

5. Any money to be paid by the Assignee pursuant to this Assignment shall be paid to the Assignor annually on or before the thirtieth day following the anniversary of the execution of this Assignment accompanied by a statement of the Net Revenues received by the Assignee during the previous twelve months.

6. The Assignor agrees to make full and complete disclosure of the Invention to the Assignee, and shall make available to the Assignee any physical embodiments of the Inventions and other data that will be or that may be useful to the Assignee in exercising its rights in the Invention.

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☎ 416.978.7833 🖷 416.978.5821 ✆ monique.mcnaughton@utoronto.ca

7. The Assignor agrees to execute, acknowledge and deliver all such further assurances and to do all such acts as may be necessary to carry out the intent and purpose of this Agreement, including without limitation, to execute powers of attorney and other documents required to maintain intellectual property protection of the Invention, and to review and provide comments with respect to such intellectual property protection when requested by the Assignee.

8. The Assignee agrees to indemnify and save the Assignor harmless from and against any loss arising out of or pursuant to any claims or demands in connection with the Invention and all costs, damages and expenses (including reasonable legal fees) incurred by the Assignor in connection therewith, except to the extent caused by the Assignor's breach of any of the Assignor's obligations herein or of any representations or warranties given by the Assignor in the Disclosure.

9. Save and except for the right to enforce the terms contained in this Assignment, the Assignor releases the Assignee from any and all claims that the Assignor may now have or may in future have in respect of the Invention.

10. This Agreement may be executed in one or more counterparts, each of which shall be deemed to be an original and all of which, together, shall constitute one and the same instrument. For the purposes of this Agreement, the signature of any party hereto evidenced by a telecopy showing such signature shall constitute conclusive proof for all purposes of the signature of such party to this Agreement.

This Assignment is made effective April 1, 2000.

Witness

Inventor(s)

Dennis G. Cvitkovitch

Peter Chun Yu Lau

Yung-Hua Li

The Governing Council of the University of Toronto

John R.G. Challis, F.R.S.C.
Vice-President, Research and Associate Provost

Louis R. Charpentier
Secretary

Appendix A

UNIVERSITY OF TORONTO CONFIDENTIAL INVENTION DISCLOSURE

Office of the Vice-President - Research and International Relations
27 King's College Circle, Room 133-S
Tel: (416) 978-7833 Fax: (416) 978-5821 email: monique.mcnaughton@utoronto.ca

1. Title of Invention

Inhibitors of peptide-mediated virulence of mutans streptococci.

2. Inventors

SURNAME, GIVEN NAMES	UNIVERSITY PERSONNEL NO.	DEPARTMENT (LIST ANY CROSS APPOINTMENTS OR AFFILIATED INSTITUTIONS)	AFFILIATION WITH UNIVERSITY (i.e. FACULTY, ASSOC., STUDENT, STAFF, VISITOR, etc.)	UNIVERSITY ADDRESS, PHONE, FAX, EMAIL
Cvitkovitch, Dennis G.	000991195	Dental Research Institute	Faculty	Rm 449A 124 Edward St. Toronto, Ont M5G 1G6
Lau, Peter C.Y.	000994382	Dental Research Institute	Staff	Rm 449 124 Edward St. Toronto, Ont M5G 1G6
Li, Yung Hua	001001925	Dental Research Institute	Staff	Rm 449 124 Edward St. Toronto, Ont M5G 1G6

3. Description of Invention

(Please highlight the novelty/patentable aspect; attach more detailed description)

See Attached:

4. How was the research funded?

SPONSOR	GRANT OR CONTRACT FUND #	INTELLECTUAL PROPERTY TERMS & CONDITIONS
National Institutes of Health	NIH # RO1 DE13230-01 U of T # 72014819	A per agreement

DATE RECEIVED: March 16, 2000 DISCLOSURE REFERENCE NO.: RIS#604
(For Research Services use only)

5. Where was the research carried out?

Faculty of Dentistry, University of Toronto

6. Is the invention related to any Material Transfer, Confidentiality or Non-Disclosure Agreement?

■ **NO** ☐ **YES** (If "Yes", please provide details)

7. Has the invention been publicly disclosed? Will it be soon?
(Please give details)

No

8. What are the potential application(s)?

See attached

9. Warranty

I/We have read, understood and agree to all of the preceeding and declare that all of the information provided in this disclosure is complete and correct. To the best of our knowledge, all persons who might legally make an ownership claim on this invention are identified in section 2.

Signature Date May 2/00
Typed Name: Dennis G. Cvitkovitch

Signature Date May 3, 00
Typed Name: Peter Lau

Signature Date Aug 3/00
Typed Name: Yung Hua Li

Signature Date
Typed Name:

For more information on University of Toronto intellectual property policies, please call 978-7833 or access http://www.library.utoronto.ca/techtran/.
For information on commercialization, patentability, protection costs, and time constraints when publication is contemplated, please call the Innovations Foundation at 978-5117.

Description of Invention:

The invention includes a group of molecules that inhibit the interaction of a 21 amino acid signal peptide with a histidine kinase- repsonse regulator that we have identified in *Streptococcus mutans*. The activation of this cell-membrane associated histidine kinase by an active signal peptide results in increased expression of virulence factors of *Streptococcus mutans*, the causitive agent of dental caries. Inhibitors of the interaction between the peptide and the receptor include peptides, antibodies or other chemical agents that disrupt this signal transduction pathway.

A molecule that specifically inhibits this cellular process can be administered to humans to limit the ability of *Streptococcus mutans* to initiate dental caries, or cause other infections including endocarditis. Inhibitors of this signal peptide may have beneficial roles when used as a prophylactic agent or when administered against acute or chronic infections.

The molecule has an advantage over current antimicrobial compounds in that its activity will be selective against the targeted organism, minimizing the likelihood that other species of organisms will acquire resistance to current protocols used for treatment of bacterial infections.

Schedule B

Patent Applications*

i)
"Signal Peptides Nucleic Acid Molecules Methods of Controlling Caries"
Inventors: Dennis Cvitkovitch; Peter C.Y. Lau; Yung Hua Li

Canadian Patent Application #2,302,861 filed April 10, 2000;
Canadian Patent Application #2,332,733 filed February 20, 2001
United States Provisional Application # 60/269,949 filed February 20, 2001 (now converted)
United States Patent Application # 09/833,017 filed April 10, 2001

and

ii)
"Signal Peptides Nucleic Acid Molecules Methods of Controlling Caries"
Inventors: Dennis Cvitkovitch; Celine Levesque; Cathy Yi-Chen Huang

United States Continuation-in-Part Patent Application # 11/005,636 filed December 6, 2004
United States Provisional application (# not yet assigned) filed December 6, 2004

* Such list of patent applications may be amended from time to time subject to the definition of Patents and Improvements herein.

Schedule C

Milestones

Milestones	Timeframe
In vitro assessment of anti biofilm potential of CSP analogs using standard microtiter plate assays that include actual colony counts of adherent organisms	Within three (3) months of the execution of this Agreement
Initiation of *in vitro* assessment of stability of lead compounds in various preparations (ie. Mouthwash, dentifrice, food additive etc.).	Within six (6) months of the execution of this Agreement
Completion of *in vitro* assessment of stability of lead compounds in various preparations (ie. Mouthwash, dentifrice, food additive etc.). Selection of lead compounds	Within eighteen (18) months of the execution of this Agreement
Initiation of an *in vitro* study to assess the *in vitro* anti-caries and anti-plaque capability of the lead compounds using an *in vitro* microbial-caries model.	Within eighteen (18) months of the execution of this Agreement
Completion of an *in vitro* study to assess the *in vitro* anti-caries and anti-plaque capability of the lead compounds using an *in vitro* microbial-caries model.	Within twenty-four (24) months of the execution of this Agreement
Initiation of an animal study to assess the *in vivo* anti-caries and anti-plaque capability of the lead compounds using one of three established rat caries models.	Within twenty-four (24) months of the execution of this Agreement
Completion of animal studies to assess the *in vivo* anti-caries and anti-plaque capability of the lead compounds using one of three established rat caries models.	Within thirty-six (36) months of the execution of this Agreement
Initiation of regulatory approval of Licensed Product by filing the necessary applications/documentation with the appropriate regulatory authorities in Canada and the United States.	Within thirty-six (36) months of the execution of this Agreement

University of Toronto

OFFICE OF THE VICE-PRESIDENT, RESEARCH AND ASSOCIATE PROVOST

ASSIGNMENT OF RIGHTS TO THE UNIVERSITY OF TORONTO BY THE INVENTOR

In consideration of the terms and mutual covenants hereinafter contained and other good and valuable consideration in the sum of Two Dollars ($2.00) of lawful money of Canada paid by each of the parties to the other, the receipt and sufficiency of which are hereby acknowledged **Dennis Cvitkovitch, Celine Levesque and Cathy Yi-Chen Huang**, and their heirs, executors, administrators and assigns (collectively the "**Assignor**") and **The Governing Council of the University of Toronto**, its successors and assigns (collectively the "**Assignee**") covenant and agree as follows:

1. As used in this Assignment, "Net Revenues" shall mean the royalty, licensing and other revenue received by the Assignee from all rights held by the Assignee in the invention entitled "**CSP Peptide Analogues**" as described in Appendix A annexed hereto (the "Invention") less legal and other fees that the Assignee incurs directly in the process of establishing and maintaining the legal protection of those rights.

2. The Assignor hereby assigns to the Assignee all right, title and interest, whatever the same may be (but without any representation or warranty as to the nature, extent or validity thereof) which the Assignor now has or may in the future have in the Invention including without limitation the right to apply for patents in Canada, the United States of America and any other country, the right to receive any letters patent that may be issued from any such applications and the right to sell, license or assign the Invention or the rights thereto.

3. In consideration of the rights granted the Assignee pursuant to this Assignment, the Assignee agrees to pay the Assignor 75% of Net Revenues.

4. If an arrangement for commercialization of the Invention is made which provides consideration to the Assignee other than cash, the parties will share the proceeds of such non-cash consideration in the same proportion as provided in paragraph 3.

5. Any money to be paid by the Assignee pursuant to this Assignment shall be paid to the Assignor annually on or before the thirtieth day following the anniversary of the execution of this Assignment accompanied by a statement of the Net Revenues received by the Assignee during the previous twelve months.

6. The Assignor agrees to make full and complete disclosure of the Invention to the Assignee, and shall make available to the Assignee any physical embodiments of the Inventions and other data that will be or that may be useful to the Assignee in exercising its rights in the Invention.

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7. The Assignor agrees to execute, acknowledge and deliver all such further assurances and to do all such acts as may be necessary to carry out the intent and purpose of this Agreement, including without limitation, to execute powers of attorney and other documents required to maintain intellectual property protection of the Invention, and to review and provide comments with respect to such intellectual property protection when requested by the Assignee.

8. The Assignee agrees to indemnify and save the Assignor harmless from and against any loss arising out of or pursuant to any claims or demands in connection with the Invention and all costs, damages and expenses (including reasonable legal fees) incurred by the Assignor in connection therewith, except to the extent caused by the Assignor's breach of any of the Assignor's obligations herein or of any representations or warranties given by the Assignor in the Disclosure.

9. Save and except for the right to enforce the terms contained in this Assignment, the Assignor releases the Assignee from any and all claims that the Assignor may now have or may in future have in respect of the Invention.

10. This Agreement may be executed in one or more counterparts, each of which shall be deemed to be an original and all of which, together, shall constitute one and the same instrument. For the purposes of this Agreement, the signature of any party hereto evidenced by a telecopy showing such signature shall constitute conclusive proof for all purposes of the signature of such party to this Agreement.

This Assignment is made effective the 22nd day of September, 2004.

Witness

Marie-Christine Kean

Marie-Christine Kean

Marie-Christine Kean

Inventor(s)

Dennis Cvitkovitch

Celine Levesque

Cathy Yi-Chen Huang

The Governing Council of the University of Toronto

John R.G. Challis, F.R.S.C.
Vice-President, Research and Associate Provost

I/s

Louis R. Charpentier
Secretary

Appendix A

UNIVERSITY OF TORONTO INVENTIONS POLICY
CONFIDENTIAL INTELLECTUAL PROPERTY DISCLOSURE

Office of the Vice-President - Research and International Relations
27 King's College Circle, Room 133-S
Tel: (416) 978-7833 Fax: (416) 978-5821 email: monique.mcnaughton@utoronto.ca

1. **Title:**

CSP Peptide Analogues

2. **a) University of Toronto Inventors/Major Contributors:**

SURNAME, GIVEN NAMES	UNIVERSITY PERSONNEL NO.	DEPARTMENT (LIST ANY CROSS APPOINTMENTS OR AFFILIATED INSTITUTIONS)	AFFILIATION WITH UNIVERSITY (i.e. faculty, res. assoc., post-doc, student, staff, visitor, etc.)	CURRENT ADDRESS, PHONE, FAX, EMAIL
Cvitkovitch, Dennis Gerard	00991195	Dental Research Institute and Institute of Biomaterials and Bioengineering	Associate Professor	Faculty of Dentistry University of Toronto Rm 449A 124 Edward St. Toronto, ON, Canada M5G 1G6 E-mail: dennis.cvitkovitch@utoronto.ca Tel.: 416-979-4917 ext. 4592 Fax: 416-979-4936
Levesque, Celine	122001498	Oral Microbiology	Post-doc	Faculty of Dentistry University of Toronto Rm 442 124 Edward St. Toronto, ON, Canada M5G 1G6 E-mail: celine.levesque@utoronto.ca Tel.: 416-979-4929 ext. 4511 Fax: 416-979-4936
Huang, Cathy Yi-Chen	981885690	Graduate department of Dentistry	Graduate student (M.Sc. candidate)	Faculty of Dentistry University of Toronto Rm 454 124 Edward St. Toronto, ON, Canada M5G 1G6 E-mail: cathy.huang@utoronto.ca Tel.: 416-979-4929 ext. 4654 Fax: 416-979-4936

DATE RECEIVED: AUG 25 2004 DISCLOSURE REFERENCE NO.: RIS 1211
(For Research Services use only)

2. **b) External Inventors/Major Contributors:**
(Please provide names and affiliations of non-University of Toronto individuals who have made a creative contribution to this Intellectual Property, i.e. sponsor employees, academic collaborators, etc.)
None

3. **Description:**
(Please highlight the novelty or patentable aspects of this Intellectual Property; attach a separate sheet if necessary)

The peptides described in the attached Table 1 have demonstrated *in vitro* activity against several properties that contribute to the ability of *Streptococcus mutans* to cause caries.

4. **How was the work leading to this Intellectual Property funded?** i.e. salaries, equipment used, supplies etc.

SPONSOR	GRANT OR CONTRACT FUND #	INTELLECTUAL PROPERTY TERMS & CONDITIONS
National Institutes of Health	5R01DE013230-05	As per NIH Guidelines

5. **Where did the work leading to this Intellectual Property take place?**

University of Toronto Faculty of Dentistry, 124 Edward St. Toronto, ON.

6. **Is this Intellectual Property subject to any software licence, material transfer, confidentiality, non-disclosure, collaboration or other agreement, written or oral, not referenced in Section 4?**
__X__NO **_____YES** (If "Yes", please provide details)

7. **What are the potential applications and/or sources of revenue from this Intellectual Property?**

The compounds have potential for anti-caries therapy.

8. **Warranty:**

I/We, the Inventors/Contributors listed in Section 2(a), have read, understood and agree to all of the preceding and declare that all of the information provided in this disclosure is complete and correct. To the best of our knowledge, all persons who might legally make an ownership claim in this Intellectual Property are identified in Section 2(a) and 2(b)

Aug 26/04
Signature Date
Typed Name: Dennis Cvitkovitch

26-08-04
Signature Date
Typed Name: Celine Levesque

Yi-Chen Cathy Huang Aug 26 04
Signature Date
Typed Name:Yi-Chen Cathy Huang

Signature Date
Typed Name:

For more information on University of Toronto intellectual property policies, please call 416-978-7833 or access http://www.library.utoronto.ca/techtran/.
For information on commercialization processes and procedures please call the Innovations Foundation at 416-978-5117.

Table 1. Effect of 5 μg/ml of peptides on competence, acid resistance and biofilm formation of *S. mutans* wild-type UA159. Peptides underlined (F1, H1, B2, C2, E2, B3) affect two or three virulence factors *in vitro*.

Peptide	Sequence	Competence	Acid resistance	Biofilm formation
CSP	SGSLSTFFRLFNRSFTQALGK	$8.19E^{-2}$	no effect	no effect
IH-1	~~S~~GSLSTFFRLFNRSFTQALGK	No effect	no effect	no effect
IH-2	SGSLSTFFRLFNRSFTQALG~~K~~	No effect	no effect	no effect
B1	S~~G~~SLSTFFRLFNRSFTQALGK	No effect	no effect	no effect
C1	SG~~S~~LSTFFRLFNRSFTQALGK	No effect	no effect	no effect
D1	SGS~~L~~STFFRLFNRSFTQALGK	↓6×	no effect	no effect
E1	SGSL~~S~~TFFRLFNRSFTQALGK	↓2×	no effect	no effect
F1	SGSLSTFFRLFNRSFTQAL~~G~~K	↓3×	↓growth	↓biomass (36.7%)
G1	SGSLSTFFRLFNRSFTQA~~L~~GK	↓2×	no effect	↓biomass (24.4%)
H1	SGSLSTFFRLFNRSFTQ~~A~~LGK	↓28,339×	↓growth	no effect
A2	SGSLSTFFRLFNRSFT~~Q~~ALGK	↓7×	no effect	no effect
B2	SGSLSTFFVLFNRSFTQALGK	↓414×	↓growth	no effect
C2	SGSLSTFFALFNRSFTQALGK	↓48×	↓growth	no effect
D2	SGSLSTFFRLFNVSFTQALGK	↓16×	no effect	no effect
E2	SGSLSTFFRLFNASFTQALGK	↓6×	↓growth	↓biomass (38.9%)
F2	SGSLSTFFRLFNRSFTQALGV	↓3×	↓growth	↓biomass (38.7%)
G2	SGSLSTFFRLFNRSFTQALGA	↓28×	no effect	↓biomass (35.6%)
H2	SGSLSTFFVLFNVSFTQALGV	nd	nd	nd
B3	SGTLSTFFRLFNRSFTQA~~LGK~~	↓8×	no effect	↓biomass (34.4%)
C3	LRSKGTQNTARFFSFSLLFGS	nd	nd	nd

Description of the assays performed

1. Competence assay.

To determine if the peptides had any impact on the development of genetic competence, *S. mutans* UA159 wild-type cells were assayed for genetic transformation. Overnight cultures were diluted (1:20) with prewarmed THYE broth and incubated at 37°C in air with 5% CO_2 for an hour. Each sample was divided into aliquots containing 1 μg of plasmid pDL289 and different concentrations of peptides (0, 0.1, 0.5, 2, and 5 μg per ml). The cultures were incubated at 37°C in air with 5% CO_2 for 3 h, gently sonicated for 10 s to

disperse the streptococcal chains, and spread on THYE plates containing kanamycin at 500 μg per ml. Plates were incubated at 37°C in air with 5% CO_2 for 48 h. Total recipients cells were counted by spreading serial dilutions on THYE agar plates without antibiotic. The transformation efficiency is expressed as the percentage of the total number of transformants over the total number of recipient cells.

2. Acid resistance assay.

The effect of peptides on acid tolerance was evaluated by assessment of growth in THYE at pH 7.5 and pH 5.5. Overnight *S. mutans* wild-type UA159 cells were diluted (1:20) with prewarmed THYE broth and incubated at 37°C in air with 5% CO_2 until an optical density of approximately 0.4 at 600 nm was reached. A 20-fold dilution was made into 400 μl of either THYE pH 7.5 or THYE pH 5.5 broth containing different concentrations of peptides (0, 0.1, 0.5, 2, and 5 μg per ml) and added in the individual wells of a 100-well Bioscreen C plate in triplicate. Wells without cells were used as blank controls. A Bioscreen microbiology reader (Labsystems, Finland) was employed to continuously grow cells and measure cell growth for 16 h at 37°C.

3. Biofilm assay.

To determine if biofilm formation was affected by the peptides, we performed a simple biofilm assay. Biofilms were developed in 96-well polystyrene microtiter plates. The growth of the biofilm was initiated by inoculating 10 μl of an overnight *S. mutans* UA159 culture into 300 μl of semi-defined minimal medium (58 mM K_2HPO_4, 15 mM KH_2PO_4, 10 mM $(NH_4)_2SO_4$, 35 mM NaCl, and 2 mM $MgSO4{\cdot}7H_2O$ supplemented with filter-sterilized vitamins (0.04 mM nicotinic acid, 0.1 mM pyridoxine HCl, 0.01 mM pantothenic acid, 1 μM riboflavin, 0.3 μM thiamine HCl, 0.05 μM D-biotin), amino acids (4 mM L-glutamic acid, 1 mM L-arginine HCl, 1.3 mM L-cysteine HCl, 0.1 mM L-tryptophan), 0.2% casamino acids, and 20 mM glucose) containing different concentrations of peptides (0, 0.1, 0.5, 2, and 5 μg per ml) in the individual wells of a 96-well microtiter plate. Wells without cells were used as blank controls. The microtiter plates were then incubated at 37°C in air with 5% CO_2 for 16 h without agitation. After the incubation, the planktonic cells were carefully removed and the plates were air dried overnight. The plates were then stained with 0.01% (wt/vol) safranin for 10 min, rinsed with sterile distilled water and air dried. Biofilms were quantified by measuring the absorbance of stained biofilms at 490 nm with a microplate reader (model 3550; Bio-Rad Laboratories, Richmond, CA).