

出國報告(出國類別：進修)

美國賓夕法尼亞大學牙科博士進修報告
研究主題:內生性恆定蛋白 DEL-1 於牙周病
緩解期促進牙周骨再生機轉

服務機關：國防醫學院三軍總醫院

姓名職稱：喻大有、少校主治醫師

派赴國家/地區：美國 賓州費城

出國期間：104 年 6 月 28 日至 108 年 6 月 1 日

報告日期：108 年 6 月 11 日

摘要

個人於104年6月28日奉派前往美國賓夕法尼亞(University of Pennsylvania)牙醫科學博士班受訓，進修目的係培訓國防醫學院牙醫學系教學研究師資，並於108年5月20日修業結束取得畢業證書後，依規定於15日內返國於國防醫學院三軍總醫院任職。本出國報告係依據行政院107年6月20日院授發管字第1071401027號函修正「行政院及所屬各機關出國報告綜合處理要點」據以撰寫，並逐一介紹進修目的、進修學校、進修系所師資、博士學程畢業要求、畢業論文簡介以及本次全職進修心得與建議，以供我國相關教學單位參考。

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壹、目的

本次進修係因國防醫學院牙醫系師資培訓之目的，個人奉國防部 104 年 6 月 3 日國人管理字第 1040008843 號令，前往美國賓夕法尼亞大學(University of Pennsylvania)牙醫科學博士班受訓，進修期程自民國 104 年 7 月 1 日至 108 年 6 月 30 日止。個人於 108 年 5 月 20 日提前取得博士學位後，旋於 108 年 6 月 3 日返校任職。

貳、進修過程

一、學校介紹

賓夕法尼亞大學(University of Pennsylvania)簡稱賓大，坐落於美國第四大城市費城西邊，是美國第一所現代意義上的大學，在 2018 年泰晤士世界大學排名中位列全球第 10 名，為美國八所長春藤聯盟創始學校之一。學校由美國開國元老 班傑明.富蘭克林於 1740 年創建，是美國第一所從事科學技術和人文教育的現代高等學校。其後賓大於 1765 年創建了全美第一所醫學院並於 1878 年成立牙醫學院。截至 2018 年底賓大共成立了 12 個學院，按成立時間分別為：文理學院(1755 年)、醫學院(1765 年)、法學院(1850 年)、工程與應用科學學院(1852 年)、牙醫學院(1878 年)、華頓商學院(1881 年)、獸醫學院(1884 年)、設計學院(1890 年)、教育研究學院(1914 年)、護理學院(1935 年)、公共政策學院(1948 年)、傳播學院(1959 年)。

班傑明.富蘭克林的創校理念為**提倡與著重實際應用的新型教育**，培養具有**創新思維、對他人的創造反應敏捷**但又不脫離現實應用的人才。這樣的教育理念貫穿賓大 279 年的發展歷程，也深深地影響個人的研究。

二、 系所簡介與師資

賓大牙醫學院是全美排名前十大牙醫學院中唯一具有獨立牙科研究機構的單位，也是全美唯一同時擁有三所聯邦政府資助研究所的牙醫學院資助項目包括基礎生物學(含幹細胞、微生物，與植物)、牙周病學、臨床止痛藥物研究。牙醫學院共計有超過 400 名專任師資，涵蓋 13 個基礎與臨床學組分別為解剖與細胞生物學、生物化學、根管治療學、口腔微生物學、口腔診斷學、口腔顎面外科暨藥理學、齒顎矯正學、口腔病理學、牙周病學、牙科公衛、兒童牙科、牙體復型、與牙科材料學組。

三、 博士學程

為取得賓夕法尼亞大學牙醫科學博士學位，所有研究生必須完成必修課程、博士資格口試與筆試、無投影片口頭研究報告(Chalk talk)、國際研討會口頭報告、畢業論文提案、公開口頭畢業答辯 等相關條件，現分述如下：

(一) 必修課程

學生必須於第一年完成所有牙醫科學進階課程，包含口腔微生物學、根管治療暨牙髓生物學、頭頸解剖學、牙科藥理學、口腔傷口癒合學、口腔診斷學、生物統計學、牙科放射線學、以及骨免疫學，在牙周病相關學組則須加修當代與經典牙周文獻回顧。另外所有博士研究生必須參加每一場牙科客座教授演講及每兩周的所內師資演講且必須於會議中提問。此外於進修期間修完至少三門與研究主題相關的外系課程。學生須於完成三個實驗室的輪訓後於第一年下學期繳交輪訓報

告，並在系主任核可與指導教授同意後選定實驗室。

(二) 年度考核、博士資格口試與筆試

年度考核與博士資格考試委員會將於學生選定實驗室後成立，目的在於及時檢視學生研究進度及協助學生解決問題，並實施年度檢核，不合格者將因無法晉級而延長進修時間。

博士資格口試與筆試則是以美國國家衛生研究院(NIH) K08 計畫申請標準審核，此階段為博士學程中最嚴苛的部分，委員們會以最高標準審視學生提出的研究計畫及時間表，在學生經歷多次退件與修正後給予口頭報告並回答問題的機會(口試)，在依據口頭報告時收到的問題完成修正後再次提交委員會審核完成筆試。此考試的目的在於訓練學生撰寫研究計畫的技巧並賦予學生應對計畫申請中各種狀況的能力。

(三) 無投影片口頭研究報告(Chalk talk)

這部分是個人覺得最特殊且有趣的部份，在經過多次會議中提問的訓練後，通過資格考試的學生會被要求在所有受過同樣提問訓練的同學前報告自己的研究，從另一端體驗被 30 個聽眾提問的經驗。講者必須在只有筆與白板的條件下於 45 分鐘內讓聽眾瞭解自己的研究並回答每一個人的提問。此考核的目的是訓練學生成為師資教學的能力。

(四) 國際研討會口頭報告

所有博士研究生都需要自己爭取在國際會議口頭報告的機會，個人有幸獲選入圍美國牙周病學會 Balint Orban Memorial Competition 決賽，並

在 2018 年美國牙周病學會舉辦的國際會議中口頭報告(見附圖四)。

(五) 畢業論文提案

研究生於指導教授同意後得以招開論文提案與請求答辯(Permission to Defense)會議，以口頭報告的方式將研究成果展現給論文委員們做初步審查。在通過委員審核後始可開始撰寫畢業論文及安排口試時間，並至少於口試前六週將畢業論文初稿遞交委員會審查。畢業論文提案至少須包含摘要、簡介、文獻探討、研究成果、研究成果對牙科臨床專業的應用，以及未來研究方向。

(六) 畢業口頭答辯

博士候選人經畢業指導委員會初步審查通過後，可開始安排畢業答辯時間，並將時間公告全校週知。委員會主席須於口試結束後 48 小時內將結果呈報研究所所長。博士候選人則須依委員意見進行實驗回答問題與畢業論文修正，俟委員們均於論文簽證表格簽署後始可辦理畢業申請事宜。學生必須完成網路畢業申請、上傳畢業論文至 Scholarly commons 等作業後始可畢業。

四、 論文簡介

牙周病是我國民眾最好發的破骨性(osteolytic)疾病之一，其最主要的臨床表癥為牙周組織發炎及骨破壞。儘管牙周菌叢失調(dysbiosis)被認為是引發牙周破壞的重要因素，病人對於去除牙周菌斑後的癒合反應卻不盡相同。近期研究顯

示宿主的發炎反應與成骨/破骨系統間的交互作用是牙周病理機轉中直接且重要的因素，但目前學界對牙周病的研究普遍著重於阻斷牙周骨破壞來“預防”牙周病，對於如何促進患者本身的自癒機轉及骨再生來“治療”牙周病則是鮮少探討。本研究著重於探討牙周病緩解期(resolution)引發牙周骨再生(bone regeneration)之機轉，從而提出可行的治療策略，以祈對改善現有牙周病治療有所貢獻。

個人主要於 George Hajishengallis教授的實驗室學習建立主要動物模型及細胞實驗。這個實驗室主要是從免疫學的角度切入研究牙周病的機轉，與個人本科非常相關。在這個實驗室主要建立的是小鼠的牙周病緩解模型，藉由在小鼠大白齒上綁5-0黑絲線，於引發小鼠慢性牙周病後將線解開移除觀察骨再生機轉。因小鼠骨代謝週期短(約五天即可觀察到成與破骨反應)、基因操作容易，在近代免疫學發展的加持下逐漸變成無法取代的優勢。然而由於小鼠的牙齒非常小，組織也非常脆弱，如何有效製造此模型對操作者是很大的挑戰。拜先前臨床經驗之賜，適應六倍放大視野時並沒有太大阻礙，在適度修正後可於一小時內完成40隻小鼠綁線的模型。在建立成骨模型後，個人將小鼠牙齦取下分析並比較其中mRNA的表達，發現內源性恆定因子DEL-1於牙周緩解期上調兩倍。這項顯著的增加暗示DEL-1在緩解期扮演著重要的生理功能。為探查其生理意義，個人引入DEL-1基因敲除小鼠牙周緩解模型，發現DEL-1基因敲除之小鼠無法再生新骨。個人更進一步發現，藉由在緩解期注射合成的DEL-1可回復緩解期骨再生。透過細胞實驗，個人證實了DEL-1可透過其特殊的功能基直接作用於成骨細胞

上從而直接促進骨生成。由於組織中內源性DEL-1表達會隨年齡下降，牙齦溝液中的DEL-1更被發現與牙周附連再生有關，個人的發現直接證實了DEL-1可作為預測牙周骨再生的重要生物指標。另一方面，因內源性DEL-1蛋白表達隨年齡下降，適時投予DEL-1預期將可達到類似回春的骨再生效果。然而由於精準的診斷仍需搭配精準的醫療才能真正改變現有醫療模式，因此個人轉向轉譯醫學研究探求可行的解決之道。

現有蛋白藥物因製藥成本高昂，導致其藥物售價及治療成本增加，從而限制了臨床治療上的使用。然而精準醫療如不考量患者的負擔能力將永遠無法真正有意義的達到精準，因此在最後的時間個人轉於Henry Daniell 教授的實驗室進行轉譯研究。藉由改造萵苣葉綠體的基因，個人成功的將人類DEL-1蛋白嵌入萵苣基因中使萵苣表達人類DEL-1蛋白，從而降低製藥成本。在可見的未來希望能投入臨床應用，搭配牙齦溝液DEL-1的精準診斷，依病人的需要投予病人負擔得起的DEL-1蛋白以精準醫療造福廣大牙周病患者。

參、心得與建議

進修心得: 感謝國防部與母校國防學院三軍總醫院的師長給予機會讓職全家能一同赴美進修，這四年的歷練使個人對牙醫科學研究的各個面向有更全面且深入的瞭解，更重要的是認識了在各個領域出類拔萃的師長與同儕。這些人脈與研究資源將有助於未來我國在牙醫科學研究領域與世界接軌。

教學建議: 這次的進修讓職體驗到不同文化與教學方法，其中無投影片口頭研究報告(Chalk talk)是個人印象特別深刻的教學模式。這堂課要求研究所內的

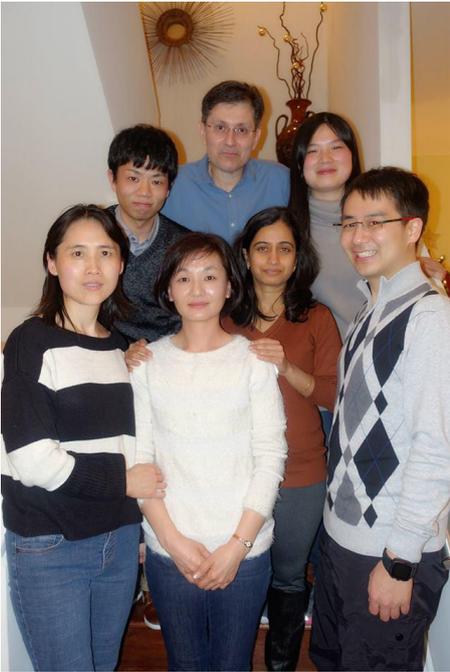
全體老師與通過格考試的學生輪流上台報告，且必須在無法撥放投影片的環境下僅以白板講述自己的研究。於此同時這門課也要求每一個研究生必須針對報告內容提問才能下課，研究所院長也會不定時參與觀察學生表現。這樣的模式除了可以訓練學生思考，也可以訓練老師教的能力。除了能增進老師與學生的互動也讓能研究生對校內研究資源有更進一步的瞭解。在現今高度講求研究績效的學術環境中，這樣的教學與互動模式不但擺脫了傳統教育形式上的束縛、給予老師授課上的彈性，更深化了教、學，與研究討論的本質，值得為我國高等教育做為參考。



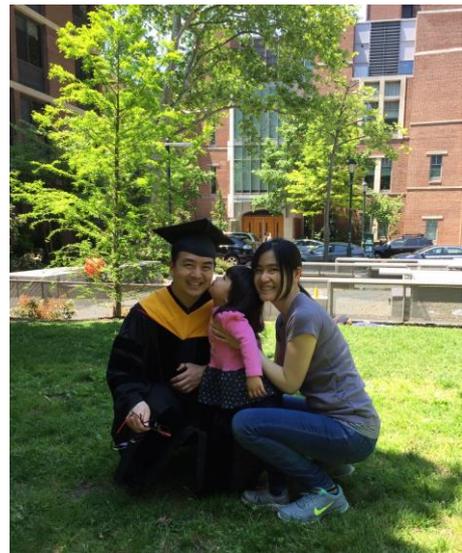
職於 108 年 6 月 14 日 0900 於國防醫學院牙醫系會議室與同仁分享進修心得。

肆、參考資料

- 一、 賓夕法尼亞大學牙醫學院網站 <https://www.dental.upenn.edu>
- 二、 Da-Yo Yuh “The Homeostatic Factor DEL-1 Promotes Periodontal Bone Regeneration During Resolution of Periodontitis” D.Sc.D. Dissertation, Department of Microbiology, University of Pennsylvania, 2019



圖一、(左)與實驗室同仁於指導教授 George Hajishengallis 家中合影。
(右)職全家與牙學院研究所院長 Dana T. Graves 合影。



圖二、職全家於校園內合影。左圖座椅左邊為賓大創校人班傑明.富蘭克林的銅像。
右圖背景為賓大牙醫學院正門。

RR

RESEARCH REVIEW: HIGHLIGHTS FROM PENN DENTAL MEDICINE 2017 RESEARCH CONFERENCES

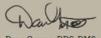
ONCE AGAIN, we were pleased to present this special research supplement to the *Penn Dental Medicine Journal*. In it are highlights from four research meetings held by Penn Dental Medicine since the start of 2017, events that brought together leading researchers and clinicians from across the country and around the world. In June of this year, Penn Dental Medicine hosted two conferences – the Penn Dental Conference 2017 and the 2nd Biennial Meeting of the International Academy for Adhesive Dentistry. The inaugural Penn Stem Cell and Regenerative Dentistry Conference just recently took place this October, and this past May, our faculty and students gathered to share their work through the School's annual Research Day – a program that demonstrated the great depth of research activities within the Penn Dental Medicine community.

Creating such forums that facilitate the exchange of ideas among investigators and help build new collaborations is a vital part of the School's mission and important to our ongoing research growth and leadership. Whether building multidisciplinary collaborations between our own basic and clinical science departments, among colleagues from the other Penn schools, or with other universities and institutions here and abroad, it is this integration of knowledge that advances the science and practice of dental medicine and other fields as well.

The impact of the School's research and scholarship in far-reaching with diverse applications. Within 2016, 160 research articles were published by Penn Dental Medicine's standing faculty members, while the depth of the School's research continued to grow through faculty recruitment. New standing faculty members joined the departments of Anatomy & Cell Biology and Oral & Maxillofacial Surgery in 2016 and the departments of Periodontics and Microbiology to date in 2017. The new recruits considerably expand Penn Dental Medicine research in the bone field as well as research in clinical microbiology related to periodontal disease and cancer. The latter is an emerging research area that links microbial infection with the behavior of cancers.

We are also building upon the academic programs that promote research – from our DScD and MSOR degree programs for postdoctoral students to our research honors, summer research program, and dual-degree opportunity in translational research for our DMD students. In addition, this year we continued to enable students and young investigators to present their work on an international stage through the School's AADR/ADR Travel Grant Award program, with 10 DMD students and six postdoctoral and junior investigators attending the 2017 AADR/ADR/CADR General Session & Exhibition.

Indeed, Penn Dental Medicine is continuing to build on its position as an international leader in the generation of new knowledge and treatment modalities in oral health and beyond.



Dana Graves, DDS, DMS
Vice Dean for Research and Scholarship, Professor, Department of Periodontics,
Director, DScD Program



Since the start of 2017, four research meetings have been held at Penn Dental Medicine, bringing together researchers and clinicians from across the country & around the world.

RESEARCH REVIEW



Research Day 2017 Celebrates Faculty, Student Research

PENN DENTAL MEDICINE brought faculty and students together to share their research activities with one another and spotlight the depth of the School's research enterprise at Research Day 2017, held May 11 at the School. This was the second year for a combined student and faculty research event, designed to show case the research being conducted throughout the Penn Dental Medicine community.

"Penn Dental Medicine Research Day now embraces all aspects and levels of research activities in the School, highlighting the great work of our faculty, junior researchers, and students," says Dr. Hyun (Michael) Koo, Chair of Penn Dental Medicine Research Day 2017. "It provides a forum for us all to learn more about each other's work."

The day's program included seven faculty presentations and two invited keynote speakers, along with a poster session what include 122 posters representing student as well as faculty/junior investigator projects.

Presenting faculty highlighted recently published research in both the basic and clinical sciences. Topics ranged from findings on the impact of diabetes on the oral microbiome (by Dr. Dana Graves, Dept. of Periodontics) and the role of the yeast bacteria interaction in early childhood caries biofilm (by Dr. Gael-su Hwang, Dept. of Orthodontics) to a study on a receptor protein that may provide new approaches to inflammatory diseases (by Dr. Hydar Ali, Dept. of Pathology) and another on linking mechanical strain to neuroinflammation (by Dr. Chana Mitchell, Dept. of Anatomy & Cell Biology).

In other faculty presentations, Dr. Henry Daniell, Dept. of Biochemistry, talked on his work using a novel drug delivery approach, sharing that biopharmaceuticals can be delivered topically in chewing gum. The chewing gum, he explained, is impregnated with enzymes and antimicrobial peptides that are produced in plant cells to disrupt biofilms that form on teeth. In addition, Dr. Shuyang (Shan) Yang, Dept. of Anatomy & Cell Biology, discussed the discovery in her lab of a new bone protein (regulator of G protein signaling protein 12) that plays a key role in osteoporosis and inflammation-caused bone loss, and Dr. Chider Chen, also in the Dept. of Anatomy & Cell Biology, reported on findings that mesenchymal stem cell therapy can effectively rescue osteoporosis and skin fibrosis in systemic sclerosis.

The day's keynote lecturers included Dr. Kam W. Leung, Samuel Y. Shang Professor of Biomedical Engineering at Columbia University, speaking on the topic of "Bioengineering of Direct Cellular Reprogramming" and Dr. Martha Sommerman, Director of the NIH's National Institute of Dental and Craniofacial Research, presenting the Joseph L. Robinson Memorial Lecture on "NIDCR Leading Advances in Oral Health Research and Innovation."

"I thoroughly enjoyed my visit to Penn Dental Medicine Research Day, which provided an opportunity for me to engage with faculty at the school and the broader campus," says Dr. Sommerman. "The quality of research presented by the students was impressive, as is the vision set forth for the school by the leadership team."

A strong representation of the current research throughout the School was featured in the poster presentation, which along with 44 faculty/junior researcher posters, included 78 student projects from the Summer Research Program, the School's honors program, the Bridging the Gaps community-internship program, and other independent student research. A faculty panel judged the student posters, presenting the Vernon Brightman Research Society Awards in first through third place (see page 43). In addition, student and postdoctoral/junior investigator research was also recognized with the awarding of the 2017 AADR Travel Grants this year to DMD students and 12 individuals representing Master of Science in Oral Biology and Doctor of Science in Dentistry residents and junior investigators received Travel Grant awards. The AADR Travel Grant program was launched by Penn



Dental Medicine in 2016 to build opportunities to advance ongoing research and leadership among students and junior researchers. This year's recipients will attend and be encouraged to present their work at the 210th AADR/CADR Annual Meeting to be held in Fort Lauderdale, FL, in March 21-24, 2018. The 2017 Joseph and Josephine Robinson Award for Excellence in Research was also presented to faculty (see page 43).

An event like Research Day can help advance research within the School in a number of ways, notes Dr. Dana Graves, Vice Dean for Research and Scholarship. "Research Day is a wonderful opportunity for researchers from different disciplines to share what they are doing and learn from each other," says Dr. Graves. "It allows students, basic research faculty, and clinical faculty to appreciate the accomplishments of each. It's a great day of exchange."

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AADR TRAVEL AWARDS ADVANCING STUDENT RESEARCH EXPERIENCE

Through the School's AADR Travel Awards, Penn Dental Medicine students and junior researchers had the chance to showcase their research on an international stage at the AADR/CADR Annual Meeting & Exhibition, March 21-24, 2018 in Fort Lauderdale. This was the fourth year for the Penn Dental AADR Travel Awards with 16 recipients participating in this year's meeting (see list below).

The AADR Travel Award program was launched by Penn Dental Medicine in 2014 to advance student/junior research, providing funds toward their travel to the annual AADR meeting where awardees have the opportunity to present their work. Recipients are selected by a faculty panel of judges at Penn Dental Medicine's annual Research Day (the 2018 AADR Travel Award grants will be presented at Research Day 2018, May 10).

The AADR Travel Awards are funded through the School's Research Incentive Fund Committee with additional support from Dentsply Sirona and Johnson & Johnson.

PARTICIPATING DMD STUDENT AWARDEES

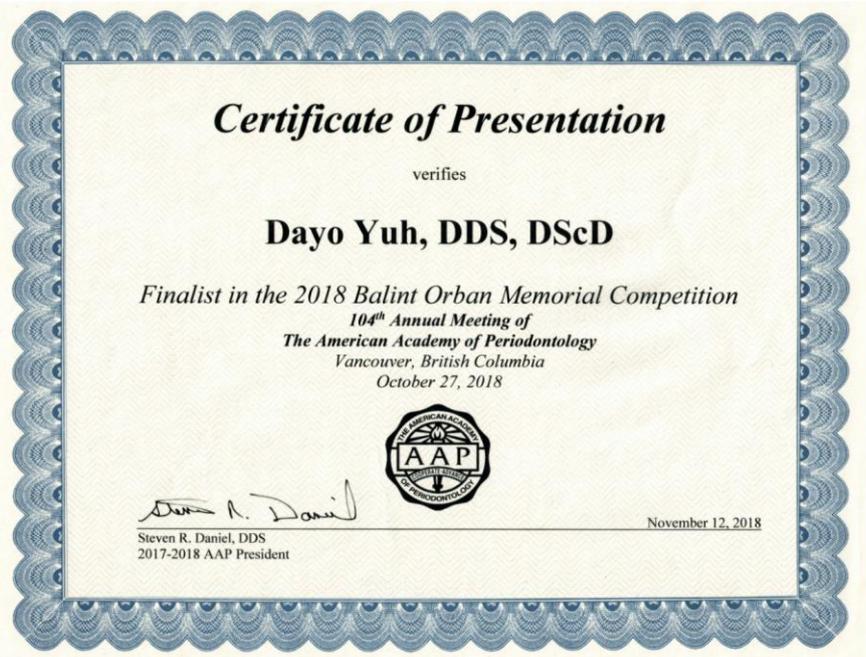
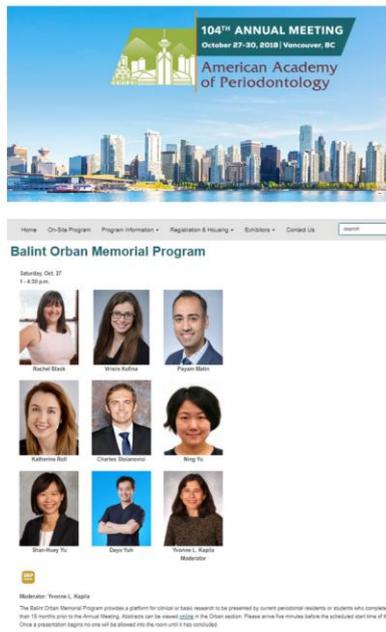
Student/Project	Preceptor
Saro Atam (D'18): <i>Bond Strength and Nanomechanical Properties of Oxzone Treated Dentin</i>	Fusun Ozer, Div. of Restorative Dentistry
Justine Chiou (D'19): <i>The ESCRT Machinery is Recruited in KSHV Assembly and Egress</i>	Yan Yuan, Dept. of Microbiology
Jerry Choi (D'19): <i>IKK-BETA Deletion in Mesenchymal Stem Cells Improves TGF-β Expression in Diabetic Fractures</i>	Dana T. Graves, Dept. of Periodontics
Lansara Jaruthien (D'19): <i>Role of SOX2 as a Downstream Effector in ESRP1-Induced Cleft Lip and Palate Formation in Mice</i>	Hyun-Duck Nah, Dept. of Orthodontics
Priyanka A. Patel (D'19): <i>Regulation of Antimicrobial Peptide-Induced Mast Cell Responses by MRGPRB2 and B-ARRESTIN2</i>	Hydar Ali, Dept. of Pathology
Abby L. Syverson (D'19): <i>Lineage Specific NF-KB Inhibition in MSCs Resolves Lymphocyte Trafficking in Diabetic Fractures</i>	Dana T. Graves, Dept. of Periodontics



PARTICIPATING GRADUATE DENTAL EDUCATION STUDENT AWARDEES

Student/Project	Preceptor
Ibrahim Alkanfari (GD'19): <i>Naturally Occurring Missense Variants of MRGPRX2 and their Effect on Mast Cell Function</i>	Hydar Ali, Dept. of Pathology
Ting-Han Chang, (GD'20): <i>The Role of Lgr5⁺ Stem-like Cells in Pathogenesis of Ameloblastoma</i>	Anh D. Le, Dept. of Oral & Maxillofacial Surgery
Andrew Henry (D'T2, M'15, GD'18): <i>Orbital Floor Fracture Repair with Polymerized 85:15 Poly(L-lactide-co-glycolide) Implants</i>	Helen Giannakopoulos, Dept. of Oral & Maxillofacial Surgery
Kenneth Kulta (M'19, GD'22): <i>A Pre-Radiation Dental Treatment Protocol for Head and Neck Cancer Patients</i>	Neeraj Panchal, Dept. of Oral & Maxillofacial Surgery
Da-Yu Yuh (GD'19): <i>DEI-1, A Coupling Factor which Promotes Bone Regeneration during Resolution of Periodontitis</i>	George Hajishengallis, Dept. of Microbiology

圖三、職與內人於在學期間積極參與賓大牙學院的研究，時常登上賓大牙學院雜誌研究版面。下圖右，職與內人曾於 2017 年於校內學術競賽同時獲獎，並獲補助參加美國牙醫科學研究年會(AADR)。



圖四、職代表賓夕法尼亞大學獲選入圍 2018 年由美國牙周病學會主辦的 Balint Orban Memorial Competition 總決賽，右圖為入圍決賽上台報告之證明。



圖五、職代表賓大牙醫學研究所及博士班參加 2019 年賓夕法尼亞大學全校畢業典禮（職胸前用於支撐博士掛袍的金色鈕釦為台灣圖樣的別針）。