The research & application of PAPP-A is beyond obstetrics, with **> 2,500 titles in PubMed by Dec. 31, 2017 (>620 for Down syndromes; >300, pre-clampsia; >293, cardiovascular). PAPP-A was first orally reported at the annual convention of FASEB (federation of medical basic sciences) on April 19, 1973 in Atlantic** City, NJ by me Tsue Ming Lin; or earlier when it (abstract) was sent for its deadline date Dec. 14, 1972 (Rf1). The convention was attended by 25,000 scientists, with hundreds meets. In one meet I reported the isolation & designation of 4 pregnancy proteins as PAPP-A, -B, -C and D; and purification of 3 (A, C & D). Portion (Characterization) of this report was soon detailed in 1974 (Rf2), which was often cited as the first reference on PAPP-A. Our work dealt with PAPPs, not PAPP-A only. Our 2 reports with the word "PAPP-A" in the title are reviews in books thus not in the PubMed title list. By our initiation of reagent exchanges & their reactivity comparison, PAPP-D was identified as the known hormone HPL; PAPP-C as SP1 reported by 2 labs in Russia & Germany years earlier; **both PAPP-A & PAPP-B as newly discovered proteins by us; & many other proteins with >12 different names (e.g., PZP) as the same protein (Rf3,4).** The PZP, not PAPP-A, is readily detectable in women taking hormone contraceptive & in late pregnancy. With similar molecular weight, same electrophoresis mobility & greater concentration, PZP would mask PAPP-A in the assay used then. An earlier article by our group on observations of multiple pregnancy proteins (PPs, PAPPs) **(Rf5)** used detecting antibodies which were not absorbed with plasma from women taking hormone contraceptive would reveal PZP but not PAPP-A. Besides, none of those PPs was named, isolated or characterized, but the article was mistaken by some as the first report on PAPP-A. For **these findings I was invited to several international meets. Four of those I participated & are memorable as briefed below..**

The **first meet**, "the 5th Meeting of the International Group for Carcinoembryonic Proteins: Placental Proteins", in Copenhagen, Denmark in August 1977, invited me & Dr. Halbert (my boss at UM). We planned to attend, but could not make the trip because the Meet could get only $ 300 for travel expense for each of us & we had just committed all $ 1500 travel funds of the NIH research grant for 4 color plates in a scientific paper (myocarditis). The Meet resulted in a report for a WHO publication, & a "Subcommittee on Pregnancy Associated Proteins of WHO" with us as corresponding members. It was organized by Drs.Horne & Rosen. We commented its draft only **(Rf6).** The group was instrumental in preparation of **International Standard Pregnancy Plasma** which promoted research & clinical application of pregnancy proteins, especially PAPP-A. The **2nd meet**, "4th International Symposium on Endocrinology of Pregnancy: Pregnancy Associated Proteins" at University of Aberdeen, Scotland in July 1978, invited me but not Dr. Halbert. He is a good speaker. I thus asked the organizer Dr. Klopper to have him in my place. The request was granted. A few weeks later, when I, but not he, received the airlines ticket for the event, I reminded Dr. Klopper of my request for replacement but he insisted that I should go with the ticket (> $1000) & Dr. Halbert could do reporting as we planned. Dr. Halbert was given another travel expenses, taking advantage of Dr. Halbert's son's working at an airlines. Dr. Klopper had me chaired a session instead & we both attended the Symposium. Reports from 11 invited speakers were published as a book "Placental Proteins" (**Rf3**). In addition to the driving -through sightseeing the city in late afternoon, the city Aberdeen (pop. 220,000 busy with the North Sea oil fields) gave a welcome civic reception in the 1st evening in its 500-year art gallery with the mayor wearing traditional Scottish dress (kilt & sporran) and his wife at its entrance. The 2nd evening was an university reception. With a few hundred of meet participants already at tables, the invited speakers were held arm by their lady companion into a decorated hall & to a long table on the stage, following a bag multi-pipe music player with traditional Scottish dress & music. The wife of University of Aberdeen medical postgraduate division dean held my arm to the stage, like in a dream & no knowing before-hand. The 3rd evening was planned to be a farewell party at the beach but, with rain, held at Dr. Klopper's house. On my way to Aberdeen, a stopover in London I took taxi to see the Buckingham palace & guard changing. Besides the airline ticket & expenses paid by the Symposium, I & Dr. Halbert received the royalty from the book, $100 each. My only earning from writing. Earlier I & Dr. Halbert had a contract with a publisher to write a book 'Cardiac Auto-immunity" with a 10% royalty, but abandoned after I completed 1st draft because I was too busy with this new research of PAPPs.

The **3rd meet**, "International Conference on Placental Proteins", in Sydney, Australia in November 1981, had the original invitation to me lost in the University of Miami mail. Half a year later, the senior organizer Dr. J.G.Grudzinskas had an Australian Qantas travel agency in Ft. Lauderdale found me at Cordis Labs of my new job.. The agent gave me the conference invitation. With only a few weeks before the conference, I ignored it. After the conference closed, Dr. Grudzinskas asked me again to write a chapter for the book that was based on the conference. He reasoned that, in view of our pioneering work in this field, the book would appear incomplete without our contribution. I had to complete the manuscript in a month, as all other authors had their reports done before the Conference for the book **(Rf4)**. The publisher gave authors 10 % discount on all its books, instead of royalty, beside a copy of the book (463 p.) free.

The 4th meet was organized by the Chinese (Taiwan) Society of Immunology & held in the Convention Center at the Veteran General Hospital in Taipei, Taiwan in August 1983. It was a 1-day Society's Annual **Meeting,** 1-day official tour & 2-day "Pre-congress **Symposium** on Human Tumor Immunology", followed immediately by the 5th International **Congress** of Immunology in Kyoto, Japan. At the **Meeting** I orally reviewed on PPs (**Rf7**). The 1-day official tour took invited speakers like I & their companions to the National Palace Museum, Tri-Service Hospital & its Medical School, National Taiwan University main campus, National Yang-Ming Medical College, etc. Most of these invited speakers were international scientists & also gave lectures at the Congress. The 2-day **Symposium** had several free sightseeing tours which I joined with my wife to the Chi-lung harbor 40 miles away, sea side rock park there & aboriginal village & show in the mountains, etc. We also went to **the banquet dinners at the Grand Hotel hosted by the Academia Sinica (National Research Institute) the 1st & at the Kuopin Hotel by the Society next evenings**. At the **Congress** in the National Kyoto Convention Center inside mountains off the Kyoto City, there was a dinner party for all 6000 guests. Most of us felt very hungry when meeting that day was over at 6 pm, rushed to the very beautiful garden, & grabbed foods & drinks at the entrance. We were full when we got to the garden proper with much better foods & drinks of many nationalities & shows on the stages & firework. The one week long Congress had free tours everyday, for which I accompanied my wife to see the old imperial palace, Nara streets, temples (1,500 in the city) & some new developments there. The tour photographers posted 5x7 photos of these tours next day at the entrance of Convention Hall. I bought out all 5 with me in the picture to avoid "embarrassment", even though I attended many meet sessions and had presented a report on the ELISA for immune complexes (a 3-min. oral with 1-hr poster presentation). I had done all I supposed to do for the meet before the auxiliary activities.

Two unexpected findings in 1990s boosted studies on PAPP-A . **The 1st one (Rf8)** led to use it as a serum marker for the 1st trimester screening &, with 2 other markers, for up to 100 % sensitivity for **Down syndrome** (trisomy 21 ; DS) & 95 % for trisomy 13 & 18 pregnancies (DSP), allowing early, more private & less traumatic termination of DSP, best at 9 weeks of gestation . PAPP-A thus helped to drop DS birth despite rise in DSP & to reduce expensive & riskier later invasive tests (amniocentesis & CVS). **The 2nd one** (**Rf9**) identified PAPP-A as **a protease** for Insulin-like Growth Factor Binding Proteins 4, & then 5 & 2 & active in cell growth & injury , leading it to roles in fetal growth, type 2 diabetes, unstable coronary plaques, serum markers for acute heart syndrome (diagnosis & prognosis), preeclampsia (early indicator), longevity, osteoporosis treatment, long-term hemodialysis (mortality predictor) & other pregnancy / fetal chromosome anomalies. The human gene for PAPP-A is on chromosome region 9q33.1. Our & other's earlier reports on its immunosuppressive & possible roles in protection of fetus from homograft rejection, on its activity in blood coagulation system, & on its analogue in animals have received less attention recently . The Mayo Found. Med. Educ, & Res. received 2 patents on PAPP-A.

Rf1: Lin et al, 'Characterization & purification of human PAPPs', Fed. Proc. 32: 623, '73. **Rf2**: Lin et al, 'Characterization of four PAPPs', Am. J. Obstet. Gynecol. 118: 223 -236, '74. **Rf3**: Halbert & Lin, 'PAPPs: PAPP-A & PAPP-B", p89-103** in "Placental Proteins"(ed. Klopper & Chard), '79. **Rf4:**Lin et al,'Identification, purification & character -ization of PAPP-A & PAPP-B', p283-312 in "Pregnancy Proteins:…', (Grudzinstas et al, ed), '82. **Rf5**: Gall & Halber, 'Antigenic constituents in pregnancy plasma …' Int Arch Allergy 42:503-515, '72. **Rf6**:Horne et al,"Human placental & pregnancy protein. Group report', WHO publ ?, '77. **Rf7**:Lin, "Immunological application & implication of pregnancy proteins', Chinese J Microb Immun 16:116-117, '83; 17:25-35, '84. **Rf8**:Brambati et al,'Ultrasound & biochemical assessment of 1st trimester pregnancy',p181-194 in "The Embryo: normal & abnormal …" (Chapman et al, ed). **Rf9**:Lawrence et al,'The insulin-like growth factor (IGF)-dependent IGF binding protein-4 protease ...is pregnancy plasma protein A', 96:3149-53,'99. **Rf10**:Lin et al, 'Pregnancy-associated plasma antigens in the rat & mouse', Proc Soc Exp Biol 145:62-66, '74. **Rf11**:Lin et al, "Measurement of PAPPs during gestation & their immunological identification', Fed Proc 33: 382, '74. **Rf12**:Lin et al. "Measurement of PAPPs during gestation', J Clin Inves -tig 54:576-82,'74. **Rf13**:Lin $ Halbert, Immunological comparisons of various human PAPPs', Int Arch Allergy 48:101-15,'75. Rf14:Lin et al,'PAPPs in human placenta',Fed Proc 34:682,'75. **Rf15**:'Lin et al',Human PAPPs during postpartum period', Am J Obs Gyn 124:382-87,'76. **Rf16**:Lin et al,'Relation of obstetric parameters to the concentrattions of four PAPPs at term in normal gestation', Am J Obst Gyn 125:17-24, '76. **Rf17**:Lin et al,'Quantitative analysis of PAPPs in human placenta',J Clin Investig 57:466-72,'76. **Rf18**:Lin et al,'Pregnancy zone protein analogue in pregnant & non-pregnant primates, & its decrease during pregnancy in some monkey species',Clin Exp Immunol 26:609-22,'76. **Rf19**:Lin & Halbert,'Placental localization of human PAPPs',Science 193:1249-52,'76. **Rf20**:Lin et al,'Plasma concentration of four pregnancy proteins in complications of pregnancy',Am J Obst Gyn 128:808-10,'77. **Rf21**:Lin & Halbert,'Immunological relationships of human & subhuman PAPPs',Int Arch Allergy 56:207-23,'78. **Rf22:Lin et al,**'Characterization & purification of PAPP-B',Int Arch Allergy 57:294-303,'78. **Rf23**:Lin et al,'PAPPs in pregnant & pseudopregnasnt rats',Int Arch Allergy 57:233-38,'78. **Rf24**:Lin et al,'PAPP-B in normal & abnormal pregnancy at term',Brit J Obst Gyn 85:652-56,'78. (See Appdx 6a/more) **Note:** PAPPs = pregnancy-associated plasma proteins; & = and; Lin et al = Tsue Ming Lin & > 2 other..

PAPP-A 的研究与應用已不只在產科学. 美國的医学網絡PubMed到2017的12月31列出>**2500有関PAPP-A的題目(>620与唐氏症; >300與孕期驚嚇前期症; >293與心血管病). PAPP-A最早公告是林祖銘**,我**於1973的三月在亞特蘭**得市的美國基礎医学会联合大会的報告,或裁止日1972的12月14日前寄給該会的摘要(**Rf1**).這大会有25,000科学家参加,分幾百小組討論会,我在其一会上報告分離及定名四个妊娠血漿蛋白質為PAPP-A,-B,-C与-D,及純化其三(A, C & D).其一部份不久詳述在1974的美國婦產科学会雜誌(**Rf2**).這文常被引述為PAPP-A的第一篇参考文献. PAPP-A在PubMed出現晚是因為我們的報告包括其他PAPP,不是只有PAPP-A而已.我有"PAPP-A在題目上的文章是在書內,PubMed不包括**(Rf3,4)**.我們發起的試劑交換及比較它們的反應性証实PAPP-D是已知的荷尔蒙HPL,PAPP-C与一两年前被苏联及德国两研究所先發現的SP1是同樣的蛋白質, **PAPP-A与PAPP-B 是我們的)新發現,12个不同名的是PZP,**這PZP在用荷尔蒙避孕藥婦女及孕婦的血漿中容易查到,它与PAPP-A有相近的分子量相同電泳速度, 在當時用的測驗法会把較少量的PAPP-A掩蓋住,使PAPP-A看或查不到, 我們实驗室較早報導孕娠蛋白質的複雜性的文章**(Rf5)**所依据的測試是用沒经過用荷尔蒙避孕药的婦女的血漿處理過的抗体試劑,会一樣的只能查看到PZP, 沒有PAPP-A的綜跡, 而且該实驗/研究也沒有對所有查看到的蛋白質定名,分離或定性,但那篇文章被某些人誤報為PAPP-A的第一个報導.因這些我被邀請去幾个國際討論会,其中四会我與会及留念如下述.

第一个会是1977八月在丹麦首都哥本哈更開的"癌胚胎蛋白質國際研究組第五次会".我与上司哈教授被邀請要参加,但沒成行,因該会最後只能給每人$300的旅宿費,而我們剛经美國衛生研究院NIH的批准把研究費内全部開会旅費$1500用在我們的一雜誌篇'心肌炎'彩色微相片的印刷.該会的報告登在世界衛生組織的某刊物**(Rf6)**並成立該組織的'孕妊娠性蛋白質次委員会';我們為其通訊委員在其草稿上出意見,該会後來推動製備了**國際孕婦血漿標準樣本**讓実験室用,幫了推廣孕娠蛋白質,尤其是PAPP-A,在臨床上的應用的研究.**第二个会**是1978七月在苏格蘭的阿伯定市開的"國際内分泌学討論会-妊娠性蛋白質".我先被邀請,我上司演講很好,我去信給主辦的盍教授請求讓我上司代替我去與会,答應了,但不久後只有我收到他寄來的來回机票(>$1000),我寫信要他改給我上司,他回信要我用那机票,他会另外安排我上司的與会,利用我上司有一子在航空公司的机会,我們都去,他演講**(Rf3)**, 我主持一節目.該会三天都有同行婦女参加的晚宴.头一晚是市長歡迎会在因北海石油再發達的阿市(人口22万)的500年博物館展覽廳内,穿古盛裝佩帶家口袋的市長夫婦在門口与進門的人招呼.第二天在大学小礼堂,两百與会人坐在餐桌後,11位被邀請来演講(講稿收集成"胎盤蛋白質")的各在一女伴牽手臂跟一位盛古裝吹着多音喇叭的進入上舞台上的長桌,女伴不上,我是阿大医学院研究部院長夫人牽我進去,像在做夢,事前沒人告訴我這儀式,到門口才知道的.,第三天是在海灘的啤酒歡送,臨時因雨搬到蓋教授家.与会人可,有些在三天裡也用"大幅廣告板"報告過他的研究.在飛阿市停留倫敦几小時我搭計程車去逛了王宮附近,看了衛兵換班儀式.除了飛机票及住吃由會負担外,我与我上司哈教授在"胎"書的出版後還各得$100.我生平唯一寫作收入. 几年前我們两人與出版商訂約寫"心臟自体免疫"一書在我寫完草稿後放棄,因太忙於這剛開始的孕娠蛋白質的研究工作

第三个会是1981的11月在澳洲細尼市的" 國際妊娠蛋白質討論会" .給我的邀請書掉失在我已不去上班但実験室及辦公室還在的邁亞密大学,當時剛在一私人实験p所開始新工作. 半年後該会的主要主負責人古博士託在羅托堡市(邁市北辺隣市)的澳洲肯達士旅行社的人找到我,給我該会的邀請信及文件.因会很迫近,我沒理它.但会開完後,古博士寫信来要我寫一篇文章放入該会的書(463頁),他說我們開拓了那一類研究,該書不能沒有我們的文章, 因為其他作者在会上已交上報告的文章,我就忽忙的寫了寄給他. 題目是" PAPP-A与PAPP-B的鑑定,純化与特性" (**Rf4**).除了送作者一本外,出版店給作者打9折買店的所有書.

第四个会是台灣中華免疫学会辦的在台北榮民医院的大会中心1983八月召開的.头一天是学会的**年会**,次日是參觀, 然後是两天的" 集会前腫瘤免疫学**討論会**' ,接着是在日本京都市的五天的第五屆國际免疫学**集会**.我在**年会**上報告了妊娠蛋白質的免疫学的應用等,其全文登在該学会的雜誌上(**Rf7**), 在付印時沒经作者我的復查, 有不少數字不全或錯誤.一天的參觀把我,我内人及邀請来演講的外賓(包括我)及他們的女伴帶去古宮博物館,三軍医院及其國防医学院,台大校總區,陽明医学院等走馬看花或看研究实驗室,這些外賓在討論会及集会都演講. **討論会**两天有給外賓女伴觀光的節目,我倍内人去逛了40哩外的基隆港,野柳海辺公國,山地村及其表演.我們也去了**中央研究院在圓山大飯店及学会在國賓旅館招待外賓与女伴的晚宴**. 在京都的**集会**是在郊外山裡的國家大会中心.有一晚宴招待所有6000與会的人及陪伴.下午六点会開完会時大家都餓了,一起衝進後花園,在门口就抓食物吃,飲料喝,入到内有更好的各種吃喝的東西時我們都已飽了,園内有舞台上有日本舞,辺上還放煙花, 集会每天都有郊遊節目,我陪了内人去逛了舊皇宮,奈良市,几个和尚廟(据說有過1500个)及新開發的, 路上有人照相,把5x7吋的相片展示在大会中心進口室内,我把有我在内的5張全買,以免別人看到不大好,我聽了几節会,做一个有関免疫複合体之酶素連接劑測試法的報告,完成与会的目的後才出去散心.

1990年代有两个新發現促進了PAPP-A的研究. **头一**个是PAPP-A是血清指標, 與其他两个共用可在在第一妊娠期近100%測出**唐氏綜合症(痴呆症;蒙古痴呆症;**染色体21有3个)及95%有3个染色体13或18的胎兒的妊娠(**Rf8**). 使有這些不良妊娠能早期並更少損傷的終止, 最好在妊娠9週時做這些. **第二个**是PAPP-A是" 類似胰島素之生長促進素4, 5及2的**蛋白質酶**" **(Rf9)**及活耀在細胞生長與損傷,因此有功用在胎兒生長,第二類糖尿病,不安定的心冠血管塊斑,急心病的血清指標(預測及診斷),早期驚嚇病之早期指標,寿命,骨鬆病治療,長期血透析之死亡預測及其他妊娠与胎兒異常染色体等. PAPP-A的基因在染免体區域9q33.1 .我們及其他人報導過的其免疫抑止及防止胎兒因異体移植被排斥,血液凝固系统上的作用,及動物類似物很少被注竟到.某医研所得PAPP-A两專利.