14)

عنوان المشروع باللغة العربية - Title of the proposed project in Arabic	في سرطان الغدة الدرقية ضعيف التمايز RAS و TERT الطفرات الوراثية في محفزات
Title of the proposed project in English	RAS and TERT promoter mutations in poorly differentiated thyroid cancer
المشرف الرئيس - PI	أماني الغامدي
التخصص الدقيق للمشرف الرئيس - Specialty of PI	كيمياء حيوية للاعصاب
المشرف المساعد - Co-PI	علي سعيد الزهراني
المدة المتوقعة لإنجاز البحث منذ الحصول على موافقة عمادة الدراسات العليا (بالشهور) - Expected time in month to finish	12 شهر
Abstract of the proposal (No more than 200 words)	The incidence of thyroid cancer is remarkably increasing. Epithelial cell-derived thyroid cancer is classified to differentiated and undifferentiated subtypes. Differentiated thyroid cancer is further classified into papillary (most common) and follicular thyroid cancer. A relatively newly recognized subtype is poorly differentiated thyroid cancer (PDTC). This subtype has intermediate grade

	between well differentiated thyroid cancer and the undifferentiated thyroid cancer (anaplastic thyroid cancer). In general, PDTC is associated with aggressive course, lymph node and distant metastasis and higher risk of morbidity and mortality. Previous molecular studies have shown that RAS mutations are the most common genetic alterations in this aggressive form of thyroid cancer. Recently, TERT promotor mutations have also been shown to be prevalent in PDTC. The relationship between these two types of genetic alterations in PDTC is unclear. We propose to study a sample (at least 100 patients) of PDTC for the rates of these alterations, compare the tumor pathology and behavior with respect to the underlying genetic defects and assess whether the presence of these types of alterations is synergistic. RAS and TERT promotor mutations are common and are likely to be synergistic with each other in poorly differentiated thyroid cancer
Hypothesis of the proposal	RAS and TERT promoter mutations are common and are likely to be synergistic with each other in poorly differentiated thyroid cancer
Specific objectives	1. Study rates of RAS (KRAS, HRAS and NRAS codons 12/13 and 61 mutations) and TERT promotor (C228T and C250T mutations) in PDTC 2. Assess the relationship between the presence of either of these mutations or both of them on the pathological features, behavior and outcome of PDTC
Methodology & Major Techniques to be used	1. DNA isolation from paraffin embedded tissue or fresh tissue of thyroid cancer 2. PCR of exon 2 and exon 5 of HRAS, KRAS and NRAS genes and TERT promoter region where two previously reported mutations were found. All of these techniques have been optimized in our laboratory 3. Direct sequencing (Sanger) 4. Collection of clinical, histopatholgical features and outcome of thyroid cancer patients 5. Statistical analysis using Standard Statistical analysis programs (e.g. SPSS)
Availability of Samples	Yes

Availability of Chemicals	Yes
Availability of Instruments	Yes
Ethical Approval	In the process
Recent References	1. Alzahrani, A.S., et al., Comparison of differentiated thyroid cancer in children and adolescents (2. Alzahrani, A.S., et al., TERT Promoter Mutations in Thyroid Cancer. Horm Cancer, 2016. 7(3): p. 165-77. 3. Alzahrani, A.S., et al., HABP2 Gene Mutations Do Not Cause Familial or Sporadic Non-Medullary Thyroid Cancer in a Highly Inbred Middle Eastern Population. Thyroid, 2016. 26(5): p. 667-71. 4. Alzahrani, A.S., et al., Single Point Mutations in Pediatric Differentiated Thyroid Cancer. Thyroid, 2016. 5. Alzahrani, A.S., et al., Uncommon TERT Promoter Mutations in Pediatric Thyroid Cancer. Thyroid, 2016. 26(2): p. 235-41. 6. Qasem, E., et al., TERT promoter mutations in thyroid cancer: a report from a Middle Eastern population. Endocr Relat Cancer, 2015. 22(6): p. 901-8. 7 Murugan, A.K., et al., Classical V600E and other non-hotspot BRAF mutations in adult differentiated thyroid cancer. J Transl Med, 2016. 14(1): p. 204. 1-Reduction of RPT6/S8 (a Proteasome Component) and Proteasome Activity in the Cortex is Associated with Cognitive Impairment in Lewy Body Dementia Alghamdi, A., Vallortigara, J., Howlett, D. R., Broadstock, M., Hortobágyi, T., Ballard, C., Thomas, A. J., O'Brien, J. T., Aarsland, D., Attems, J., Francis, P. T. & Whitfield, D. R. 21 Mar 2017 In : JOURNAL OF ALZHEIMERS DISEASE. 57, 2, p. 373-386 2- Decreased Levels of VAMP2 and Monomeric Alpha-Synuclein Correlate with Duration of DementiaVallortigara, J., Whitfield, D., Quelch, W., Alghamdi, A., Howlett, D., Hortobágyi, T., Johnson, M., Attems, J., O'Brien, J. T., Thomas, A., Ballard, C. G., Aarsland, D. & Francis, P. T. 30 Nov 2015 In : JOURNAL OF ALZHEIMERS DISEASE. 50, 1, p. 101-110 3- Depression and Synaptic Zinc Regulation in Alzheimer Disease, Dementia with Lewy Bodies, and Parkinson Disease Dementia

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4- Assessment of ZnT3 and PSD95 protein levels in Lewy body dementias and Alzheimer's disease: association with cognitive impairment
Whitfield, D. R., Vallortigara, J., Alghamdi, A., Howlett, D., Hortobágyi, T., Johnson, M., Attems, J., Newhouse, S., Ballard, C., Thomas, A. J., O'Brien, J. T., Aarsland, D. & Francis, P. T. Dec 2014 In : Neurobiology of Aging. 35, 12, p. 2836-2844

5- Dynamin1 concentration in the prefrontal cortex is associated with cognitive impairment in Lewy body dementia.
Julie Vallortigara,a,1 Sindhoo Rangarajan,1 David Whitfield,1 Amani Alghamdi,1 David Howlett,1 Tibor Hortobágyi,2 Mary Johnson,3 Johannes Attems,3 Clive Ballard,1 Alan Thomas,3 John O'Brien,4 Dag Aarsland,5 and Paul Francis1