

4. Members of the consortium

4.1 Participants

Participant 1. International Agency for Research on Cancer (IARC) France

Description of participating institute

Research expertise and research environment

The International Agency for Research on Cancer (IARC) is the specialized cancer agency of the World Health Organization. The objective of the IARC is to promote international collaboration in cancer research, and it is involved in both epidemiological and laboratory research. IARC has been a leader in head and neck cancer research for over 20 years, and is the coordinating partner of the ARCAGE in Europe, and InterCHANGE in South America. IARC continues to hosts the database and biorepository of ARCAGE and InterCHANGE.

Overview of research activities

The Genetic Epidemiology Group (led by Dr Brennan) is involved in identifying both lifestyle and genetic factors associated with cancer through a variety of population based studies. This includes large-scale whole-genome scans of common cancers, with a particular focus on head and neck cancers, lung cancer and kidney cancer. Dr Brennan has also led research activity into the role of HPV in head and neck cancer and leads the head and neck cancer cohort consortium.

Role in the proposal and relevant infrastructure

IARC will be the coordinator of the HEADSpAcE consortium. IARC's expertise in coordinating large scale genomics research across countries and organizations, and its independent role as an international organization facilitates this activity. In addition, the close working relationship with IARC's parent organization, WHO, allows the research findings of the proposed project to be translated effectively into timely policies for cancer control. IARC also houses an important cancer biorepository, including ARCAGE and InterCHANGE.

Role of key scientific people

Dr Paul Brennan (male)

Dr Brennan is a leader of WP9 (management). As Head of the Genetic Epidemiology Group at IARC, Dr Brennan's primary area of work is conducting large scale multi-partner epidemiological studies to identify genetic and molecular risk factors for human cancers. Much of this involves coordination and collaboration within large scale international consortia, such as ARCAGE and InterCHANGE, and the international head and neck cancer consortium, a cohort consortium project funded through the NCI of 12 cohorts that aims to elucidate the role of HPV biomarkers in head and neck cancer. He is a PI of the Mutograph project, a recently funded CRUK 'Grand Challenge' initiative that aims to recruit and whole genome sequence 5000 cases of cancer from across the world. He has over 500 publications including 38 as first author, 47 as second author and 70 as last (or corresponding) author.

Dr Ghislaine Scelo (female)

Dr Scelo is the leader of WP1 (Coordination of biorepositories and data). She has been a Scientist in the Genetic Epidemiology Group since 2009, where she has been in charge of coordinating several multicenter cohort and case-control studies, including follow-up of cases for outcome. She has been in charge of developing the associated large biorepositories. She has been the PI of a large kidney cancer genome-wide association study which implemented gene expression data together with germline data in the statistical models (US NCI R01). She is also a key epidemiologist partner in cancer genomics projects, including European kidney cancer project of the International Cancer Genome Consortium (FP7 EC) and the multicancer CRUK Grand Challenge mutational signature project.

She has over 80 articles (16 as first author or co-first author; 10 as last author) – Times cited: 1,935 – Average citations per item: 24.7 – H-index: 26. Complete bibliography: <https://www.ncbi.nlm.nih.gov/sites/myncbi/1XkJaa9sagkQw/bibliography/42397323/public/?sort=date&direction=ascending>.

Dr James McKay (male)

Dr McKay is the Group Head of IARC's the Genetic Cancer Susceptibility (GCS) group and will be involved in the genetic analysis involved in the WP6, particularly the analysis of rare genetic variants derived germ-line exome sequencing. Dr McKay has twenty years of experience in the field of molecular genetics carrying out familial studies (linkage analysis) and carried numerous genetic association studies of cancers of the lung, head and neck and kidney, as well as several types of lymphoma. Having published in excess of 180 papers, including high impact journals such as Nature, Nature Genetics, JNCI, AJHG and PLoS Genetics. Dr McKay has been involved in the head and neck cancer research, notably assessing the contribution of the *ADH* genes (Hashibe et al, Nat Genetics 2008), 15q25 (Chen et al, CEBP 2011), the first UADT cancer GWAS (McKay et al, PLoS Genetics 2011) and most recently implicated a rare variant in *BRCA2* (K3326X) in lung (Wang et al, Nat Genetics 2014) and UADT cancers (Delahaye et al, JNCI 2015).

Recent, relevant publications

1. Lesseur C, Diergaarde B, Olshan AF, (...) **McKay JD, Brennan P**. Genome-wide association analyses identify new susceptibility loci for oral cavity and pharyngeal cancer. *Nat Genet.* 2016 Dec;48(12):1544-1550
2. McKay JD, Hung RJ, (...) Chanock S, **Brennan P**, Landi MT, Amos CI. Large-scale association analysis identifies new lung cancer susceptibility loci and heterogeneity in genetic susceptibility across histological subtypes. *Nat Genet.* 2017 Jul;49(7):1126-1132
3. Kreimer AR, *et al*. Evaluation of human papillomavirus antibodies and risk of subsequent head and neck cancer. *J Clin Oncol.* 2013;31(21):2708-2715
4. **Brennan P**, Wild CP. Genomics of Cancer and a New Era for Cancer Prevention. *PLoS Genet.* 2015 Nov 5;11(11)
5. Perdomo S, Avogbe PH, Foll M, Abedi-Ardekani B, Facciolla VL, Anantharaman D, Chopard P, Calvez-Kelm FL, Vilensky M, Polesel J, Holcatova I, Simonato L, Canova C, Lagiou P, **McKay JD, Brennan P**. Circulating tumor DNA detection in head and neck cancer: evaluation of two different detection approaches. *Oncotarget.* 2017 Aug 7;8(42):72621-72632

Relevant projects

1. The role of germline and somatic DNA mutations in oral and oropharyngeal cancers (VOYAGER) – Supported by the US National Institute of Dental and Craniofacial Research (NIDCR) R01 grant, USD 3,131,954, PI: Brennan, P (primary), Hayes, N; Diergaarde, B. 2017-2021.
2. HPV Cancer Cohort Consortium (HPVC3) – Supported by US National Cancer Institute (NCI) U01 grant, USD 1,862,053, PI: Brennan, P. 2015-2019.
3. Alcohol Related Cancer and Genetic Susceptibilities in Europe (ARCAGE) – Supported by EC RTD FP5 grant, EUR 2,085,727, PI: Brennan, P. 2002-2005.
4. International Study on Cancer of the Head and Neck, Genetics and Environment in Latin American Countries (InterCHANGE) – supported by IARC, PI: Brennan, P and Scelo, G. 2017-2022.
5. Mutographs of cancer: discovering the causes of cancer through mutational signatures – supported by CRUK, GBP 4,520,875. 2017-2022.

Infrastructure and facilities available for HEADSpAcE

The IARC biobank holds one of the largest, most versatile, collections of human biospecimen in the World, currently including 5 million biological samples from 1.5 million individuals. The biobank has a specific objective in promoting scientific collaboration and has developed a clearly defined pipeline for how investigators outside of IARC can access relevant samples. The storage facilities include liquid nitrogen (LN2) tanks and freezers (-80°C, -40°C, -20°C) and fridges. LN2 tanks (storage conditions -196°C) contain blood derived fluids kept in plastic straws from the ARCAGE and InterCHANGE studies and are directly available for the HEADSpAcE project.

Participant 2.**Catalan Institute of Oncology (ICO)****Spain****Description of participating institute****Research expertise and research environment**

The project will be developed within the Catalan Institute of Oncology (ICO) (<http://www.iconcologia.net>), which is a public non-profit institute, created in March 1995 and assigned to the Catalan Health Service (CatSalut). ICO is a leader in cancer care in Catalonia, with a high international recognition. Its approach to the disease is comprehensive, combining all in one organization, prevention, care, specialized training and research. ICO comprises four centers (L'Hospitalet, Badalona, Girona and Tarragona i Terres de l'Ebre) and is an oncology referral for almost 45% of the adult population of Catalonia. Research and innovation for a better future is one of its values. ICO is structured in 4 programs (Cancer epidemiology, Hereditary cancer, Translational research/ProCURE Program and Cancer Prevention and Control Program), and each program is fully equipped in order to meet with the basic need of the investigators. ICO is one of 50 Comprehensive Cancer Centers throughout Europe. A rich, stimulating and multidisciplinary environment and a fertile scientific humus for biomedical research are provided not only by ICO, but also by other local actors (hospitals, scientific parks, non-profit health research centers and research-driven biotech companies) acting in strict cooperation with ICO. According to the SCImago 2017 report, ICO ranks percentile 35th in research and 18th in innovation. The average number of publications between 2012 and 2016 is 354 per year and the average impact factor is 6. Moreover, 722 clinical trials were active with 10 as promotor and more than 960 patients in clinical trials. ICO has a long record participation in research and innovation projects funded by the EU. Currently, ICO researchers are involved in 1/FP7 project (Health), 7/H2020 (ERC, Health, ICT, INFRAIA, EURATOM), 4/3rd Health Program (exSANCO), 1 ERA-NET TRANSCAN and 1 SUDOE.

Overview of research activities

The Cancer Epidemiology Research Program (CERP) at ICO is devoted to research on the causes, epidemiology, early diagnosis and prevention of cancer. CERP provides advice on the design, development and assessment of cancer prevention strategies, such as providing assessments of population-based cancer screening programs, and providing estimates of cost-effectiveness of health promotion programming and cancer prevention measures. With demonstrated expertise in the areas of laboratory, clinical and population-based methods, CERP has become internationally recognized for conducting high quality research, while its scientists have made cutting-edge discoveries and noteworthy contributions to the field of cancer epidemiology. CERP is composed of four major units: Information and interventions in infections and cancer Unit; Molecular epidemiology and genetics in infections and cancer Unit; Laboratory of infections and cancer; and Nutrition and Cancer Unit. The units involved in the present proposal are the laboratory and the Molecular epidemiology and genetics in infections and cancer Unit. The latter has as major goals: (1) To assess the etiological factors of the anogenital, head and neck, lymphoma and leukemia giving special attention to the infection agents and environmental and genetic susceptibility; (2) To study the natural history from acquisition of infections to cancer, focusing on the molecular bases; and (3) to develop and evaluate new techniques and algorithms of clinical diagnosis, prognosis and prevention of these cancers.

Role in the proposal and relevant infrastructure

Main tasks in the project: ICO team will lead WP4 regarding the identification of the extent of HPV-driven OPC in Europe and LA, and assessment of lifestyle, clinical and genetic predictors of OPC and its influence on clinical outcome. Moreover, the team will participate in WP3 and will provide cases from several projects that are ongoing to achieve goals of some of the WPs. Projects from ICO:

- (1) ICO head and neck survey: This is a cross-sectional study of cancer cases diagnosed from 1990 to 2012. Total amount of cases: 3,680 paraffin embedded cases from oral cavity (1,264), pharynx (1,374), and larynx (1,042). Higher representation from South America and Europe;
- (2) Retrospective cohort on oropharyngeal cancer patients: Diagnosed from 1990 to 2013. Total amount of cases: 788;
- (3) Prospective cohort on oropharyngeal cancer patients: Diagnosed from September 2016 onwards. Until today, we have included 40 patients.

The team has infrastructure to achieve the objectives proposed in the project. It has a multidisciplinary team of epidemiologists, statisticians, biologists, technicians, and additional personnel supporting the research team. In addition, it has a laboratory specialized in the study of molecular basis of infections related to cancers.

How it matches the proposal: One of the main lines of research from the CERP at ICO is head and neck cancers, its etiology, and potential biomarkers of prevention and that can be used as prognosis and predictive factors.

Role of key scientific people

Dr Laia Alemany (female)

Dr Laia Alemany will lead WP4. She is a public health physician and epidemiologist from Barcelona, Spain. She is a medical graduate from the University of Barcelona, has a Master in Public Health from the Universitat Pompeu Fabra, Barcelona and a Master of Molecular Oncology from the Centro Nacional de Investigaciones Oncológicas. She completed her specialty training in preventive medicine and public health through the Hospital Vall d'Hebron Training Program. Currently, she is Chief of the Molecular Epidemiology and Genetics in Infections and Cancer Unit, and acting Chief of the Cancer Epidemiology Research Program at the Catalan Institute of Oncology. The Unit is composed of 4 epidemiologists, 4 statisticians, 1 biologist and 1 oncologist; and the Program of more than 50 person staff. She has been coordinating during the last 10 years an international project on HPV burden in HPV-related cancers. This project has assembled more than 20,000 paraffin preserved primary tumors from 50 countries worldwide, including anogenital and head and neck cancers. She has participated in the organization of the project, protocol design, recruitment of cases, and other derived tasks; and noteworthy in the coordination of a team composed by epidemiologists, statisticians, biologists, pathologists, technicians devoted to this project. In the context of this project, she has also been able to interact with international research groups that have participated in the study, and has organized annual steering committee meetings with the main aim of overseeing the project. In parallel, the last 5 years she has built and coordinated a retrospective cohort of approximately 1,000 oropharyngeal cancer patients from 4 Spanish hospitals, and currently starting a prospective cohort of oropharyngeal cancer patients in order to assess diagnostic and prognostic markers.

Dr Marisa Mena (female)

Dr Marisa Mena received her bachelor's degree in chemistry in 1999 from the University of Barcelona. She holds a cum laude PhD degree in biomedical sciences (University of Barcelona, 2006) and a master's degree in international health (tropEd ErasmusMundus Program of European Commission, 2011) where she conducted an evaluation of the impact of a breast cancer awareness program in rural Ghana.

She joined the Cancer Epidemiology Research Program in 2012. Her research interests focus on the epidemiology and prevention of cancers with a known or potential association to infections and/or immunosuppressant conditions. Currently, she is involved in several projects aimed at ascertaining the role of HPV infection in HPV-related cancers.

Sara Tous (female)

Sara Tous received her degree in statistics in 2001 from the Universitat Politècnica de Catalunya, Barcelona. From 2001 to 2003, she was working for the Catalan Centre of Innovation and Business Development as a data manager for the Department of Quality Control (Catalonian Government). In 2005, she started working at the Catalan Institute of Oncology (ICO). She received her specialization in sciences and techniques in statistics in 2008 from the Universitat Politècnica de Catalunya, Barcelona and over the last 10 years, Sara has been involved in research of statistical regression models to study the relationship between anogenital and head and neck preneoplastic lesions and cancers and HPV infection in UNIC. She is a member of different groups (AGAUR, HPV VVAPO, RIS HPVTT) supporting research of the relationship between HPV and genital and head and neck preneoplastic lesions and cancers. Research area specialty: Statistics, descriptive analysis, regression models, logistic regression, multilevel regression models, survival analysis, Cox regression (proportional hazards models).

Dr Miren Taberna (female)

Miren Taberna is medical oncologist, responsible for clinical research and clinical assistance of the Head and Neck Tumor Functional Unit of the ICO / H. Bellvitge. Its healthcare activity focuses on conducting a medical oncology consultation for patients with head and neck tumors, as well as coordinating the different Clinical Trials in which patients participate and going to the different tumor committees. She is also involved in research studies regarding the assessment of prognosis biomarkers in head and neck cancers. Dr Miren Taberna has completed a master's degree in molecular oncology (CNIO), benefited from a Rio Hortega-SEOM scholarship during which he completed her doctoral thesis and completed (among others) a stay at the HPV Cancer and Cancer Laboratory of Sant Jaime Center (Dr. Maura L Gillison, Ohio).

Dr Miquel Angel Pavon (male)

Dr Miquel Angel Pavon graduated in biology (UAB) and PhD in Biomedicine (UB), has extensive experience in the development of molecular markers in cancer patients, especially in head and neck tumors, having carried out studies using transcriptomic and genomic tools to identify mechanisms and markers involved in resistance to treatment, dissemination and tumor recurrence, in HPV-associated and non-HPV associated tumors. MA Pavón, after joining the Catalan Institute of Oncology as a chief of the Infections and Cancer Laboratory (INCA-Lab) in 2016, has adopted as its main line of research the study of the molecular mechanisms involved in the HPV infection process, persistence and invasive progression and has extended its research to all neoplasms associated with HPV. The main objective of his research is to develop new biomarkers that can be transferred to clinical practice, improving the prevention, early diagnosis and treatment of HPV-associated tumors. He recently completed a stay in the National Cancer Institute where he has been trained in the used of Next Generation Sequencing methods for the analysis of HPV genome.

Recent, relevant publications

1. **Mena M***, **Taberna M***, **Tous S**, (...) **Pavon MA**, Bravo IG, de Sanjosé S, Bosch FX, **Alemany L**. (*)Co-first authors. Double positivity for HPV-DNA/p16(ink4a) is the biomarker with strongest diagnostic accuracy and prognostic value for human papillomavirus related oropharyngeal cancer patients. *Oral Oncol*. 2018 Mar;78:137-144
2. **Taberna M**, **Mena M**, **Pavón MA**, **Alemany L***, Gillison ML*, Mesía R*. (*)Co-senior authors. Human papillomavirus related oropharyngeal cancer. *Ann Oncol*. 2017 Oct 1;28(10):2386-2398
3. Martel M, **Alemany L**, **Taberna M**, **Mena M**, **Tous S**, Bagué S, Castellsagué X, Quer M, León X. The role of HPV on the risk of second primary neoplasia in patients with oropharyngeal carcinoma. *Oral Oncol*. 2017 Jan;64:37-43
4. Castellsagué X*, **Alemany L***, (...) **Tous S**, (...) **Mena M**, (...) Bosch FX, on behalf of the ICO International HPV in Head and Neck Cancer Study Group. (*)Co-first authors. HPV involvement in head and neck cancers: comprehensive assessment of biomarkers in 3,680 cases. *J Natl Cancer Inst*. 2016 Jan 28;108(6)
5. Ndiaye C*, **Mena M***, **Alemany L**, (...), de Sanjosé S, Trottier H. (*)Co-first authors. HPV DNA, E6/E7 mRNA, and p16^{INK4a} detection in head and neck cancers: A systematic review and meta-analysis. *Lancet Oncol*. 2014 Nov;15(12):1319-31

Relevant projects

1. Prognostic and predictive markers of HPV in oropharyngeal cancer patients. PERIS, Pla Estratègic de Recerca en Investigacions Sanitàries, 2016-2020. PERIS SLT002/16/00404. PI: Laia Alemany. Duration: 2017-2020.
2. Detection of antibodies against HPV16 E6 oncoprotein: validation of a new and promising screening biomarker for the prevention of HPV-driven oropharyngeal cancer. Fondo Investigaciones Sanitarias. Instituto de Salud Carlos III. PI15/01205. PI: Xavier Castellsagué/Laia Alemany. Duration:2015-2018.
3. Use of HPV markers as prognostic factors in oropharyngeal cancer patients. Acadèmia de Ciències Mèdiques de Catalunya i Balears. PI: Laia Alemany. Duration: 2016-2018.
4. Assessing the role and prognosis of Papillomavirus in patients with cancer of the oropharynx. Fondo Investigaciones Sanitarias. Instituto de Salud Carlos III. PI1102096. PI: F. Xavier Bosch. Participation: Laia Alemany-Researcher and coordinator. Duration: 2011-2015.
5. Role of human papillomavirus infection and other co-factors in the etiology of head and neck cancer in India and Europe (HPV-AHEAD). 7th Framework Program. HEALTH-F2-2011-282562. Local PI: F. Xavier Bosch. Participation: Laia Alemany-Researcher and coordinator. Duration: 2011-2015.

Infrastructure and facilities available for HEADSpAcE

The infrastructure and facilities available in the participating centers are adequate to carry out the requested project. Infection and Cancer Unit at CERP, ICO and participating hospitals: The research group is composed of a multidisciplinary team of professionals with extensive experience in design, coordination and analysis of epidemiological studies (epidemiologists, clinicians, biologists, graduates and graduates in statistics, computer science, administrative and doctoral students). In particular, UNIC has a local computer network with connection to the general network of the CSUB and has a computer network with its own server. At the infrastructure level, it has offices, a meeting room and a conference room.

ICO's Translational Research Laboratory: The laboratory has an approximate area of 850 m2 distributed in areas of 825771 HEADSpAcE – Part B

general laboratory, pre and post PCR areas, engine room, cold room, study rooms, offices and a common crop area with the rest of the center's research groups. It has extensive laboratory equipment. With respect to computer equipment, the laboratory has computers in a local network with direct access to the Internet through its own server, scanner with transparency accessory, BN and color printers, conventional software, image and data analysis and an automatic sequencing service.

Laboratory of Infections and Cancer: Cytology and Virus and Cancer laboratories have staff and contracted researchers, senior technicians, FPII technicians and fellows. It was created in 1998 and from the beginning the laboratory has worked intensely in the comparison, validation and reproducibility of different HPV detection techniques (PCR, HC-I, HC-II, Reverse blot test, Linear Array, SPF-10, DEIA , LiPA25, Anyplex) in cytological samples and fresh tissue and preserved in paraffin, applying standardized protocols and strict quality controls. In the area of cytological diagnosis, immunocytochemistry techniques applied to diagnosis have been implemented and techniques in development such as automated reading and liquid cytology have been evaluated.

Clinical functional units of ICO / H. Bellvitge: These units are staffed by highly qualified clinical staff in both their care work and translational research. The functional unit guarantees the best treatment for our patients, since all choice and realization of it is approached from a multidisciplinary group. This is reflected in the multidisciplinary nature of our group. In addition, the possibility of collaboration between several pioneer centers in this pathology, guarantees a rapid recruitment of patients in a short period of time, facilitating the obtaining of short-term results, as well as the implementation of them later in the usual clinical practice, and the viability of ongoing studies and the continuation of future studies. Successful previous collaborations have already been made with the members of all the functional units, which guarantee the coordination of the project.

Participant 3.**University of Turin (UNITO)****Italy****Description of participating institute****Research expertise and research environment**

The University of Turin (UNITO) is one of the largest Italian Universities, with about 70.000 students, 3.900 employees (academic, administrative and technical staff), 1.800 post-graduate and post-doctoral research fellows. Research and training are performed in 27 Departments, encompassing all scientific disciplines. According to ARWU international ranking, UNITO is ranked among the top 300 universities out of 1.200, together with other five Italian universities. With reference to the most recent national evaluation of the Italian university system, UNITO is ranked second in the area of medical sciences. As for internationalization, UNITO is involved in about 450 international cooperation formal agreements with institutions from all around the world (South America, Mediterranean countries, India and China, in addition to Europe), including joint educational programs at undergraduate and doctoral level. The long record of participation of UNITO in the EU strategic research agenda results from 115 FP7 funded research project and 67 projects funded under H2020.

The Department of Medical Sciences of UNITO accommodates the Cancer Epidemiology Unit (CEU), one of the main Italian epidemiological research centers. CEU is placed at the University Hospital Città della Salute e della Scienza di Torino, the main hospital of the city of Turin.

Overview of research activities

CEU has a large experience in cancer research and in quantitative methods. It has been conducting etiological and clinical studies on several cancer sites, including head and neck, lung, testicular, prostate and childhood cancers. The Unit has a long tradition in coordination of and participation in large national and international epidemiological studies and is responsible for large population-based cohorts. CEU includes a Laboratory of Molecular Epidemiology with expertise in molecular biology techniques, and specifically on DNA methylation and viral carcinogenesis.

Role in the proposal and relevant infrastructure

CEU will participate in the WP1, WP2, and WP5, primarily by contributing to the recruitment of patients newly diagnosed with a head and neck cancer, participating with the ARCAGE study, and contributing to the conduction, statistical analysis and interpretation of DNA-methylation analyses.

Role of key scientific people**Dr Lorenzo Richiardi (male)**

Dr Richiardi is associate professor in Epidemiology and Biostatistics at UNITO. His main research interests are in cancer epidemiology, life-course epidemiology, molecular epidemiology and causal inference methods. He is currently the UNITO's PI of two Horizon2020 projects. He is the PI of the Italian NINFEA birth cohort, the Turin center of the Piccolipiù cohort and an ongoing project on methylation in prostate cancer, funded by the Italian Association for Cancer Research. He is involved in a number of international consortia, including TECAC on testicular cancer, INHANCE on head and neck cancer and PACE on DNA-methylation in birth cohort studies. He is co-director of the European Educational program in Epidemiology.

Dr Franco Merletti (male)

Dr Merletti is full professor in Epidemiology and Biostatistics at UNITO and the Director of CPO Piemonte (Regional Centre for Prevention in Oncology) and CEU at the Hospital "Città della Salute e delle Scienze" in Turin. He is a cancer epidemiologist, and has coordinated and participated in a large number of population-based studies and consortia on occupational, environmental and life-style exposures, including ARCAGE, INHANCE, CHCOS, MOBI-Kids and GERoNiMO. He is or has been a member of international and national bodies including the Panel for Social Medicine in the EU, the Italian National Oncological Commission, the IARC Monograph Program, the European Education Program in Epidemiology.

Dr Milena Maule (female)

Dr Maule is assistant professor in Epidemiology and Biostatistics at UNITO. Her main research interests include environmental and occupational risk factors, determinants of survival in cancer epidemiology, and methodological

research. She participates in international multicentric studies or consortia, including MOBI-Kids, GERoNIMO, I4C.

Dr Daniela Zugna (female)

Dr Zugna is assistant professor in Epidemiology and Biostatistics at UNITO, with strong expertise in biostatistical methods and specifically on causal inference methods, and mediation analysis. She has been involved in the international project CASCADE on HIV seroconversion. She is involved in the EU-funded project LIFeCycle and collaborates in projects on diagnosis and prognosis of prostate cancer and melanoma.

Recent, relevant publications

1. Abrahão R, Anantharaman D, (...) **Merletti F, Richiardi L**, (...) Boccia S, Gheit T, Tommasino M, Scelo G, Brennan P. The influence of smoking, age and stage at diagnosis on the survival after larynx, hypopharynx and oral cavity cancers in Europe: The ARCAGE study. *Int J Cancer*. 2018 Feb 6. doi: 10.1002/ijc.31294. [Epub ahead of print]
2. Giraldi, L, Leoncini, E, (...) **Richiardi, L**, Boffetta, P, Hashibe, M, Lee, Y, Boccia, S Alcohol and cigarette consumption predict mortality in patients with head and neck cancer: A pooled analysis within the International Head and Neck Cancer Epidemiology (INHANCE) Consortium. *Ann Oncol*. 2017 Nov 1;28(11):2843-2851
3. Popovic M, Fasanelli F, Fiano V, Biggeri A, **Richiardi L**. Increased correlation between methylation sites in epigenome-wide replication studies: impact on analysis and results. *Epigenomics*. 2017 Dec;9(12):1489-1502
4. D'Souza G, Anantharaman D, (...) **Merletti F**, Boccia S, Tajara EH, Zavallos JP, Levi JE, Weissler MC, Wright S, Scelo G, Mazul AL, Tommasino M, Brennan P. Effect of HPV on head and neck cancer patient survival, by region and tumor site: A comparison of 1362 cases across three continents. *Oral Oncol*. 2016 Nov;62:20-27
5. Lesueur C, Diergaard B, (...) **Richiardi L**, Boccia S, Polesel J, (...) Amos CI, McKay JD, Brennan P. Genome-wide association analyses identify new susceptibility loci for oral cavity and pharyngeal cancer. *Nat Genet*. 2016 Dec;48(12):1544-1550

Relevant projects

1. ARCAGE is a multicentric case-control study on head and neck cancer, coordinated by the IARC, that involves over 2,000 cases and 2,000 controls recruited between 2002 and 2005 in 10 European countries. Questionnaire data, blood samples and tumor tissue are available. ARCAGE participates in a number of international initiatives and consortia. Follow-up of the cases is available up to 2015. CEU was responsible for the ARCAGE Turin center.
2. The INHANCE consortium is an international collaboration pooling more than 30 head and neck cancer studies. It involves over 26,000 cases and 34,000 controls with questionnaire data and, for the majority of the subjects, biological samples.
3. MOBI-Kids is an EU-funded prospective case-control study conducted in 14 countries to assess the potential effects of exposure to radiofrequency and extremely low frequency fields from mobile phones and other environmental exposures on the development of brain tumors among children and adolescents. CEU coordinates the study in Italy
4. TECAC is an international consortium of molecular epidemiology studies of testicular cancer, with the aim of investigating genetic determinants of testicular cancer and gene-environmental interactions. CEU is involved in the consortium through a case-control study on testicular cancer conducted in the province of Turin
5. The CEU is responsible for an ongoing program on DNA-methylation and prostate cancer diagnosis and prognosis. The program involves a series of case-control and cohort studies of patients whose biopsies are stored at the Pathology ward of the University Hospital Città della Salute e della Scienza di Torino. CEU also collaborates to multicentric studies on biomarkers for survival of prostate cancer.

Infrastructure and facilities available for HEADSpAcE

CEU has the computational requirements (hardware and software) to store, process and analyze data with high performance, security, stability and control. The Molecular Epidemiology Laboratory of CEU is part of a cluster of laboratories with core facilities. The laboratory is fully equipped to adequately process and store biological samples and to perform molecular biological analyses The laboratory has 4 Thermal Cyclers for PCR and Real Time PCR

analyses, electrophoresis equipment, PyroMark Q24 MDx pyrosequencing, freezers at -20 °C and -80 °C, and liquid nitrogen tanks at -196 °C. CEU benefits of UNITO facilities and infrastructure necessary to conduct the project.

A Technician to be recruited according the National Italian Law. Contract (full-time), level D, specifically recruited for support to the recruitment of patients and handling of the samples as well as for support of molecular analyses.

Participant 4.**Charles University (CUNI)****Czech
Republic****Description of participating institute****Research expertise and research environment**

Charles University of Prague is one of the oldest universities in Europe, it was founded in 1348 as the first Studium generale north of the Alps and east of Paris. It had four faculties: theology, liberal arts, law, and medicine, now 1st Faculty of Medicine. As such, it is also the oldest medical faculty in Central Europe. First Faculty of Medicine with almost 1,200 staff members and 3,400 students represents the largest medical faculty in the Czech Republic. Faculty is heavily investing in research infrastructure. Our laboratories take advantage of virtually all state-of-the-art technologies that are in hands of enthusiastic staff with an international experience and reputation. Funding generated by scientific activities recently represents the majority of the Faculty budget.

In 1897, Institute of Hygiene at the Medical Faculty (now Institute of Hygiene and Epidemiology, First Faculty of Medicine, Charles University) was founded.

Now Institute of Hygiene and Epidemiology have been collaborating on several multicentric studies with International Agency for Research on Cancer since 2000. Our institute also has collaboration with NCI, NATO and some other universities in Europe.

Overview of research activities

Our researchers participate on several studies not only on cancer epidemiology research but also on toxicology (e.g. toxic metals), occupational risk factors (e.g. chemicals in occupational environment, shiftwork as a risk factor, etc.), nutritional toxicology, nutrition in childhood & breastfeeding as a prevention of chronic diseases, smoking as a risk factor of civilization diseases, quality of indoor environment etc.

Some European projects e.g. Eastern Europe Case Control Study of Kidney cancer (NCI,IARC 2000-2002), HOPE – Health Optimization Protocol for Energy-efficient Buildings (FP 5, TNO, 2001-2004), EnVIE - Co-ordination action on Indoor Air Quality and Health Effects (FP 6, IDMEC, 2004-2006), WELAS -Women in Europe Against Lung Cancer and Smoking (2007 – 2009).

Several local/national projects supported by the national grant agencies (Grant Agency of the Ministry of Health of the Czech Republic, Ministry of the Environment of the Czech Republic, Grant Agency of Academy of Science of the Czech Republic)

Role in the proposal and relevant infrastructure

Our institute will participate on WP1 and WP2, on recruitment of new cases, collecting information, taking biological samples, and follow up, as well as in WP8 (dissemination) with a particular focus of dissemination of HEADSpAcE activities in Czech Republic and regional countries.

Role of key scientific people**Dr Ivana Holcatova, PhD (female)**

Dr Holcatova is assistant professor at the Institute of Hygiene & Epidemiology, for last twenty years she is focus on cancer epidemiology. She was principal investigator in several national projects (esp. epidemiological aspects of pancreatic cancer) and also key national investigator in international projects.

Dr Jan Betka, PhD (male)

Dr Betka is assistant professor at the Department of Otorhinolaryngology Head and Neck Surgery of the 1st Faculty of Medicine, Charles University and Faculty Hospital Motol in Prague. He is specialized on anticancer immunity and endoscopic methods in ENT.

Recent, relevant publications

1. Perdomo S, Anantharaman D, (...) **Holcatova I**, Simonato L, Canova C, Lagiou P, McKay JD, Brennan P. Genomic analysis of head and neck cancer cases from two high incidence regions. *PLoS One*. 2018 Jan 29;13(1):e0191701
2. Perdomo S, Avogbe P, (...) Vilensky M, Polesel J, **Holcatova I**, Simonato L, Canova C, Lagiou P, McKay

- JD, Brennan P. Circulating tumor DNA detection in head and neck cancer: evaluation of two different detection approaches. *Oncotarget*. 2017 Aug 7;8(42):72621-72632
3. Allenson K, Castillo J, San Lucas FA, Scelo, G., (...) **Holcatova I**, (...) Brennan P, Hanash S, Li D, Maitra A, Alvarez H. High prevalence of mutant KRAS in circulating exosome-derived DNA from early-stage pancreatic cancer patients. *Ann Oncol*. 2017 Apr 1;28(4):741-747
 4. Mohelnikova-Duchonova B, Strouhal O, Hughes DJ, **Holcatova I**, (...) Funel N, Lemstrova R, Soucek P. SLC22A3 polymorphisms do not modify pancreatic cancer risk, but may influence overall patient survival. *Scientific Reports*. 2017;7(43812). DOI: 10.1038/srep43812,
 5. Muller D, Johansson M, Zaridze D, Moukeria A, Janout V, **Holcatova I**, Navratilova M, Mates D, Midttun O, Ueland PM, Brennan P, Scelo G. Circulating Concentrations of Vitamin B6 and Kidney Cancer Prognosis: A Prospective Case-Cohort Study. *PLoS One*. 2015 Oct 27;10(10):e0140677

Relevant projects

1. **ARCAGE – Alcohol Related Cancer and Genetic Susceptibilities in Europe** (FP 5, IARC 2002-2005) multicentric international study
2. **CAGEKID – Cancer Genomics of the Kidney** (EU FP7, 2010 – 2014)
3. **Multicenter case-control study of Occupation, Environment and Lung Cancer in Central and Eastern Europe** (IARC 1999-2001) multicentric international study
4. **LUN – Early stage non-small cell lung cancer study** (IARC, 2011 – 2015)

Infrastructure and facilities available for HEADSpAcE

Teaching and research at our faculty cover almost the entire spectrum of medicine and health professions from the full range of basic sciences through clinical specialties. Some disciplines are unique to our school at the national level. We prepare future medical doctors, scientists and health professionals in a modern and friendly fashion. Since we are not only a teaching, but also a research institution, we bring to education the most modern findings and technology.

In institute are laboratories for the blood processing and storage (deep freezers), we have excellent contacts to clinics with ongoing collaboration on several small projects.

Participant 5.**German Cancer Research Center (DKFZ)****Germany****Description of participating institute****Research expertise and research environment**

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) is a foundation under public law and a member of the Helmholtz Association of National Research Centers (Helmholtz-Gemeinschaft Deutscher Forschungszentren, HGF). As a national research center (more than 3000 employees), it is financed by the Federal German Government, the State of Baden-Wuerttemberg, as well as external research grants. In addition, DKFZ is part of the cooperative association of the Tumor Center Heidelberg/Mannheim. The overall mission for DKFZ is to systematically investigate the mechanisms of cancer development and to identify cancer risk factors. The results of this basic research provide the basis for developing new approaches in the prevention, diagnosis, and treatment of cancer.

Overview of research activities

The Research Program Infection, Inflammation and Cancer is one of seven research programs of the DKFZ. The Molecular Diagnostics of Oncogenic Infections Division (acting Head Dr Michael Pawlita) is one of six departments within this research program and encompasses about 30 people in three research groups.

The focus of the research group headed by Dr Tim Waterboer (15 people) is to define the role of infectious agents in cancer development by molecular epidemiology; to develop high-throughput, multiplexed diagnostic assays, and to translate biomarker discoveries into clinical practice. The group has pioneered the development of multiplex serology assays for a broad variety of infectious disease biomarkers. These assays are applied in many international projects on infection and cancer with leading epidemiological groups, including multiple studies with the US National Cancer Institute (NCI) as well as the International Agency for Research on Cancer (IARC).

Role in the proposal and relevant infrastructure

DKFZ will participate in WP3 and WP4. In particular the research group of Dr Tim Waterboer, has developed multiplex Luminex-based human papillomavirus (HPV) serology, a fluorescent bead-based high-throughput method that allows analyzing up to 2000 serum or plasma samples per day for antibodies to up to 100 different HPV protein antigens simultaneously (Waterboer et al, Clin Chem 2005). Using this method, we have completed several large case-control studies on head and neck cancer (e.g., Ribeiro et al, Int J Epidemiol 2011, Anantharaman et al, JNCI 2013) and nested case-control studies embedded in prospective cohort studies such as EPIC (Kreimer et al, JCO 2013) and PLCO (Kreimer et al, JNCI 2017). These studies have shown that antibodies to the E6 oncoprotein of HPV 16, the predominant HPV type involved in oropharyngeal cancer (OPC), are strongly associated with OPC, at the time of diagnosis, and more than 10 years prior to diagnosis. Multiplex HPV serology was compared to routine clinical biomarkers of HPV-driven OPC, such as HPV in situ hybridization (ISH) and p16 immunohistochemistry (IHC) (e.g. Lang-Kuhs et al, Cancer 2017) and laboratory-based gold-standard assays (HPV16 E6*I mRNA, e.g. Holzinger et al, IJC 2017) and found to be extremely sensitive (>90%) and specific (>95%). However, the fluorescent bead-based technology underlying multiplex HPV serology (Luminex) is not readily available in most routine clinical labs. Thus, we have developed a low-cost enzyme-linked immunosorbent assay (ELISA)-based HPV16 E6 screening assay for the early detection of HPV-driven cancers with similar characteristics as the multiplex serology assay. The ELISA only requires laboratory instrumentation that is available in standard hospital-based labs. This novel assay also detects antibodies to HPV16 E6, and has been piloted at the Catalan Institute of Oncology (ICO, Dr Laia Alemany). The assay will be implemented in Work Packages 3, 4, and 7. Staff of the partner sites will be centrally trained in an HPV ELISA summer school at the DKFZ in Heidelberg (WP3), and serological analyses of the study samples will be performed locally (WP3, 4 and WP7). In addition, random sets of locally collected sera will be re-tested in Heidelberg using gold-standard Luminex-based multiplex serology to validate the local ELISA results. Furthermore, an international standard serum for results harmonization across participating centers will be developed and provided.

Role of key scientific people**Dr Tim Waterboer (male)**

Dr Waterboer is head of the laboratory-based Infections and Cancer Epidemiology research group in the Molecular

Diagnostics of Oncogenic Infections Department belonging to the Infection, Inflammation and Cancer Research Program at the German Cancer Research Center (DKFZ). He has developed the HPV16 E6 screening ELISA that is a key technology for this application, and has successfully applied multiplex serology in various international collaborations with leading epidemiological groups, including NCI and IARC. As a trained biochemist and epidemiologist, he has the background and expertise to successfully carry out the proposed work. Dr Waterboer has published more than 170 peer-reviewed papers, including publications in the *Lancet Oncology*, the *Lancet Infectious Diseases*, the *Journal of the National Cancer Institute*, and the *Journal of Clinical Oncology*. In summary, Dr Waterboer has demonstrated a record of successfully accomplished large sero-epidemiological research projects, and the ability to lead the proposed serological analyses.

Recent, relevant publications

1. Kreimer AR, Johansson M, (...) Pawlita M, Brennan P, **Waterboer T**. Kinetics of the Human Papillomavirus Type 16 E6 Antibody Response Prior to Oropharyngeal Cancer. *J Natl Cancer Inst*. 2017 Aug 1;109(8)
2. Lang Kuhs KA, Kreimer AR, (...) Hildesheim A, **Waterboer T***, Ferris RL*. Human papillomavirus 16 E6 antibodies are sensitive for human papillomavirus-driven oropharyngeal cancer and are associated with recurrence. *Cancer*. 2017 Nov 15;123(22):4382-4390 *Co-corresponding authors
3. Holzinger D, Wichmann G, (...) Pawlita M, **Waterboer T**. Sensitivity and specificity of antibodies against HPV16 E6 and other early proteins for the detection of HPV16-driven oropharyngeal squamous cell carcinoma. *Int J Cancer*. 2017 Jun 15;140(12):2748-2757
4. Schroeder L, Wichmann G, (...) Pawlita M, Dietz A, **Waterboer T**, Holzinger D. Antibodies against human papillomaviruses as diagnostic and prognostic biomarker in patients with neck squamous cell carcinoma from unknown primary tumor. *Int J Cancer*. 2018 Apr 1;142(7):1361-1368
5. Kreimer AR, Johansson M, **Waterboer T**, Kaaks R, (...) Riboli E, Hildesheim A, Boeing H, Pawlita M, Brennan P. Evaluation of human papillomavirus antibodies and risk of subsequent head and neck cancer. *J Clin Oncol* 2013 Jul 20;31(21):2708-15

Relevant projects

1. Aids Fonds, Netherlands, Reference No. 2014209 (principle investigator: M. Schim van der Loeff, GGD Amsterdam), 01/01/2014-12/31/2017 (ongoing). Virological and serological predictors of high-grade anal intraepithelial neoplasia (HGAIN) in HIV-infected men who have sex with men (MSM). Role: Co-Investigator. This project investigates whether a number of biomarkers are predictive for HGAIN (high-grade anal intraepithelial neoplasia), i.e. persistent high-risk HPV infections; HPV anal viral load; and L1, E6, and E7 seropositivity.
2. Acción Estratégica en Salud (Spanish Government) (principle investigator: Laia Alemany, ICO), 10/01/2016-12/31/2018. Detection of antibodies against HPV16 E6 oncoprotein: validation of a new and promising screening biomarker for the prevention of HPV-driven oropharyngeal cancer. Role: Co-Investigator. This study is a first-stage proposal of a wider project aiming at the development and implementation of a low-cost screening assay based on HPV16 E6 serology for the early detection of HPV-driven cancers. The overall purpose of this study is to initiate the validation of the assay for OPC.
3. NCI, NIH, 1U01CA195603 (PI: Paul Brennan, IARC), 01/01/2016-12/31/2019. Biomarkers of human papillomavirus infection and risk of two increasing cancers consortium project (HPVC3). Role: Co-Investigator. The major goal is to evaluate the validity of HPV16 antibodies against E6 antigens as a pre-diagnostic biomarker for both oropharynx and anal cancer, with a particular focus on populations with high incidence of HPV-driven oropharynx cancer, namely in the US and Northern Europe.
4. NIDCR, NIH, 1R01DE025712 (PI: Paul Brennan, IARC), 01/10/2017-12/31/2021. The role of germline and somatic DNA mutations in oral and oropharyngeal cancers (VOYAGER)
5. Role: Co-investigator. The major goal of this project is to assess the role of genetic factors in oral cavity and oropharyngeal cancers.

Infrastructure and facilities available for HEADSpAcE

Overall, the department of Molecular Diagnostics of Oncogenic Infections encompasses 634 m². The research group of Dr Tim Waterboer occupies two laboratories of each 58 m² and has unconditioned access to common facilities of the department of about 300 m². The laboratories of the department are P2 safety level. All equipment needed for the serological analyses within this project are available in the laboratories of the department. Aside from standard laboratory equipment, these are specialized devices like e.g. 6 Luminex Analyzers (Luminex 100, 4 x Luminex 200, MagPix) and an ELISA reader. Service core facilities available at the DKFZ include electron microscopy, DNA and 825771 HEADSpAcE – Part B

protein sequencing, spectroscopy, oligonucleotide synthesis, library, and animal housing.

The research group of Tim Waterboer has competences in the development and use of Luminex-based multiplex serology as well as of ELISA for more than 10 years and the personnel is highly experienced in performing these serological analyses.

Participant 6.**University of Glasgow (UGLA)****United
Kingdom****Description of participating institute****Research expertise and research environment**

Founded in 1451, the University of Glasgow (UGLA) has a tradition of excellence as the fourth oldest university in the UK. It is a member of the elite Russell Group of leading UK research universities and a founding member of Universitas21. UGLA has fostered the talents of seven Nobel laureates, Scotland's first female medical graduates, and includes among its alumni, some of the world's most renowned innovators, from scientist Lord Kelvin, economist Adam Smith, to the pioneer of television John Logie Baird. Ranked 51st in the world (QS World University Rankings 2013) and 17th in the UK, UGLA is a world-leading research intensive institution, attracting scholars from more than 130 countries worldwide each year. The institution's annual research income totals more than £177M, which places it in the UK's top 10 earners for research. In recognition of its employment practices that specifically support the careers of women in science, technology, engineering, math and medicine (STEMM) in higher education, UGLA has been awarded an Athena SWAN Institutional Bronze Award. The Institution also holds an 'HR excellence in research' award.

UGLA's College of Medical, Veterinary & Life Sciences (MVLS) was created in 2010 bringing together three former biomedical faculties (over 400 academic staff). This major restructure has brought significant benefits for both research and enterprise activities with big investments in people (67 senior academics and 131 early career researchers recruited since 2010) and infrastructure (over £100 million invested in research infrastructure and facilities). To focus our research strategy on areas of international excellence, we have organized our research into seven research institutes between which there is a high degree of integration and collaboration of basic and translational scientists and clinicians. We also actively engage in teaching, learning and mentorship of the next generation of scientists and clinicians through the School of Life Sciences and the professional schools: School of Medicine, Dentistry, and Nursing and the School of Veterinary Medicine.

Overview of research activities

The Head and Neck Cancer Epidemiology group in the School of Medicine, Dentistry and Nursing is led by Prof Conway. This work involves investigations of socioeconomic inequalities across the cancer continuum from the burden and risk associations, to prevention and early detection, and to clinical outcomes and survival. The research involves the following methodological approaches and expertise: epidemiological analyses, big data / data-linkage, human factors and behavioral science, community trials, and systematic reviews / meta-analyses. The group works closely with IARC, the International Head And Neck Cancer Epidemiology (INHANCE) consortium and Cochrane Oral Cancer Group.

Role in the proposal and relevant infrastructure

UGLA will lead WP2 (Socioeconomic, logistic, and biological predictors of delayed head and neck cancer diagnosis), and be involved in WP1 and WP8. This includes developing protocols for late diagnosis, pooling, and subsequently analyzing epidemiological data from across European and Latin American centers. It will involve new cohort data collection in Glasgow collected in collaboration (locally) with NHS Greater Glasgow & Clyde Clinical Research Facility (research nurse pool) and Head and Neck Cancer Managed Clinical Network – this infrastructure has previously been successfully used (Prof Conway) on two EU funded studies (ARCAGE and HPV-AHEAD). In addition, qualitative methods expertise (Dr Ross) will be employed to undertake healthcare system center-level studies via a planned PhD studentship, which will benefit from support of UGLA MVLS graduate school training infrastructure.

Role of key scientific people**Professor David Conway (male)**

Prof. Conway is Professor of Dental Public Health, Honorary Consultant in Public Health in NHS National Services Scotland, and Joint Oral and Dental Specialty Group lead for NHS Research Scotland. As lead of the head and neck cancer epidemiology research group he has over 60 peer-reviewed publications on the topic. He is a founding member of the International Head And Neck Cancer Epidemiology (INHANCE) consortium, the International Centre for Oral Health Inequalities Research and Policy (ICOHIRP), and recently re-established (and chairs) the West of Scotland 825771 HEADSpAcE – Part B

Managed Clinical Network Research Group. The main focus of the research is socioeconomic inequalities and HPV in head and neck cancer research and he has been the UGLA PI on EU funded ARCAGE head and neck cancer case-control and HPV-AHEAD ARCAGE HPV follow-up study. .

Dr Alex McMahon (male)

Dr McMahon is a Reader in Epidemiology at UGLA, and an Honorary Consultant in Epidemiology with the Information and Statistics division of the NHS. He is involved in projects in the fields of public health inequalities, cancer epidemiology, and data linkage. He is skilled in designing and analyzing cohort studies and randomized controlled trials. He has been on the editorial board of *Pharmacoepidemiology and Drug Safety* and has published 119 papers.

Dr Alastair Ross (male)

Dr Ross is a Chartered Ergonomist and Psychologist and Lecturer in Behavioral Science. The main focus of his research, for which he received around £3m of funding, is studying the resilience of health service delivery systems in both Primary and Secondary care. He is currently studying opportunistic oral cancer screening in practice and the implementation of Clinical Guidelines for examination for head and neck cancer. He is deputy lead for Patient Management and Health Promotion in the School, and a founding member of the national reference group for Dentistry in the Scottish Patient Safety Program.

Recent, relevant publications

1. Purkayastha M, **McMahon AD**, Gibson J, **Conway DI**. Trends of oral cavity, oropharyngeal and laryngeal cancer incidence in Scotland (1975-2012) - A socioeconomic perspective. *Oral Oncol*. 2016 Oct;61:70-5
2. **Conway DI**, Brenner DR, **McMahon AD**, (...) Brennan P. Estimating and explaining the effect of education and income on head and neck cancer risk: INHANCE consortium pooled analysis of 31 case-control studies from 27 countries. *Int J Cancer*. 2015 Mar 1;136(5):1125-39
3. Furness S, (...) **Conway DI**. Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy. *Cochrane Database Syst Rev*. 2011 Apr 13;(4):CD00638
4. **Conway DI**, et al. Human Papilloma Virus (HPV) Oral Prevalence in Scotland (HOPSCOTCH): A Feasibility Study in Dental Settings. *PLoS One*. 2016 Nov 18;11(11):e0165847
5. Arnold M, Rentería E, **Conway DI**, Bray F, Van Ourti T, Soerjomataram I. Inequalities in cancer incidence and mortality across medium to highly developed countries in the twenty-first century. *Cancer Causes Control*. 2016 Aug;27(8):999-1007

Relevant projects

1. Human Papilloma Virus and Upper-aerodigestive tract cancer (HPV-AHEAD). World Health Organization International Agency for Research on Cancer. Seventh Framework Program (FP7) of the European Commission in the Cooperation Work Program - Health 2011 (£17,917) 2012-2014 (PI Conway)
2. Evaluation of national oral health improvement programmes. Scottish Government Health Directorate (£1,000,000) 2013-2016 (Co-PI Conway)
3. HPV Oral Prevalence in Scotland (HOPSCOTCH) feasibility study. CSO (£215,000) 2013-2015 (PI Conway)
4. Opportunities for Oral Cancer Screening. NHS Education for Scotland (£105,000) 2014-2018 (PI Conway)
5. NHS National Services Scotland. NSS PhD Studentships (£105,000) 2014-2019 (PI McMahon)

Infrastructure and facilities available for HEADSpAcE

NHS Greater Glasgow and Clyde Clinical Research Facility (nurse pool). West of Scotland Head and Neck Cancer Managed Clinical Network Research Group.

Robust information governance systems (data security protocols) are in place. Access to quantitative and qualitative analytical statistical software packages and expertise.

MVLS College Graduate School Postgraduate research facilities and training resources.

Participant 7.**University of Bristol (UBRIS)****United
Kingdom****Description of participating institute****Research expertise and research environment**

The University of Bristol (UBRIS) is a Russell Group University and one of the most prestigious universities in the UK. It is a thriving international community combining excellence in research and innovation with a vibrant entrepreneurial culture. Research is at the heart of the University's mission and accounts for its international reputation. UBRIS organizes its academic affairs across six faculties: Engineering, Science, Biomedical Sciences, Health Sciences, Social Sciences and Law, and Arts. The 2014 UK Research Excellence Framework (REF2014) confirmed its position in the top 10 UK research universities, measured by both research output and research impact. Over 33% of the University's research was judged to be 'world leading', and over 80% of publications were judged to be 'internationally excellent'. UBRIS was placed in the top 5 institutions for research impact in 10 areas. The University participates in hundreds of international collaborations both within and outside of Europe. Measured by the share of funding to date it is ranked in the top 20 participating institutions within the EU under Horizon 2020. The UBRIS Population Health Science Institute is a new center that builds on Bristol's internationally-leading reputation for research in the determinants and consequences of ill-health. The Institute's research ranges from basic discovery science in molecular and genetic epidemiology to innovative clinical trials and policy-influencing and assessment activities. The center's multi-disciplinary community spans several Schools and Faculties within the University and tackles a wide range of questions about health and health care.

Overview of research activities

UBRIS work will be based within two research groups that are part of University of Bristol Population Health Science Institute. These are the Lifecourse Epidemiology and Population Oral Health Research Group (LEPOH) based in Bristol Dental School and the Medical Research Council Integrative Epidemiology Unit (MRC IEU) based in Bristol Medical School. **LEPOH** is led by Professor Andy Ness and comprises academics with expertise in epidemiology, health psychology, nutrition, social science and statisticians, as well as clinicians and research nurses. The four main research themes are facial disfigurement, head and neck cancer, life-course determinants of health, and nutrition. Included within these are Head and Neck 5000 (a DNA backed clinical cohort of 5,500 people with head and neck cancer), and the NIHR Bristol Biomedical Research Centre Nutrition Theme. The **MRC IEU** is led by Professor George Davey Smith and integrates molecular, cellular, clinical and population data to optimize the identification of causal effects of potentially modifiable factors on disease incidence and progression using methods such as Mendelian randomization. In the Unit's recent successful renewal, it set aims to focus on studies of disease progression and the identification of 'omics biomarkers to aid prediction of disease outcome, with the view that these studies will produce findings of direct relevance to disease treatment. Alongside these and embedded within the MRC IEU, the **CRUK Integrative Cancer Epidemiology Program** aims to test the causal effects of potentially modifiable exposures and intermediates with cancer risk and progression. This program is closely affiliated with the MRC IEU and extends expertise in dealing with large-scale cancer datasets. The MRC IEU includes the Bristol Bioresource Laboratories (BBL), which provide biosample management and governance of over 2 million samples, including the Head and Neck 5000 DNA samples. It specializes in follow up and bespoke data collection of 'omics data, including genome wide SNP array data. The unit also houses a dedicated informatics team with full access to the University of Bristol's High Performance Computing facilities and has experience of management, storage and analysis of large-scale datasets. The NIHR Biomedical Research Centre and the MRC IEU work closely to translate findings from these causal analyses into interventions to improve population health.

Role in the proposal and relevant infrastructure

UBRIS will be involved in WP5, and will lead WP6. Both of these WorkPackages will use blood, DNA and tissue collected in head and neck 5000 to carry out exome analysis, as well genome wide association studies, and epigenetic studies using the samples available in the Head & Neck 5000 bioresource that combines socio-demographic, clinical and outcome data on over 5000 people with head and neck cancer. UBRIS will lead WP6 and coordinate the genome-wide analysis of 3000 HNC cases, in collaboration with IARC. This work package will utilize substantial computational infrastructure at the University of Bristol (high-performance compute cluster with >5,000 cores and associated research data storage facility for data analysis and storage) and the MRC IEU (server virtualization platform for web application deployment). UBRIS will also contribute surgical and pathology expertise to WP8.

Role of key scientific people

Professor Andy Ness (male)

Professor Ness is a Professor of Epidemiology. He leads the Lifecourse Epidemiology and Oral Health Research Group (LEPOH) and is head of research at the Bristol Dental School. He was director of the UK NIHR Biomedical Research Unit in Nutrition, Diet & Lifestyle (including Obesity) from April 2012 – 2017 and is now nutrition theme lead within the NIHR Bristol Biomedical Research Centre. He is the chief investigator on the Head and Neck 5000 clinical cohort study.

Dr Miranda Pring (female)

Dr Pring is a Consultant Senior Lecturer in Oral Maxillofacial Pathology. She is member of the Head and Neck 5000 scientific team and is responsible for development and maintenance of the study tissue resource. She currently contributes to several externally funded multi-center studies.

Professor Steve Thomas (male)

Professor Thomas is Professor in Oral and Maxillofacial Surgery. He is member of the Head and Neck 5000 scientific team and is study lead for clinical aspects of the study including liaison with collaborating clinicians and diagnostic and outcome coding.

Professor Nicholas Timpson (male)

Professor Timpson is a Professor of Genetic Epidemiology. He currently holds a prestigious Wellcome Trust Investigator Award and is principal investigator of the Avon Longitudinal Study of Parents and Children. He has just completed a MRC funded program within the IEU (which matured into his current Wellcome funded, IEU affiliated, program) focusing on the development and application of recall by genotype studies. He has extensive experience of genome wide association studies and Mendelian randomization.

Mr. Tom Dudding (male)

Mr. Dudding is a dentist and a Wellcome Trust Clinical Research Training Fellow. His work includes the application of Mendelian randomization approaches to assess the causal impact of vitamin D on head and neck cancer. He also has experience working with large scale 'omics datasets including the genetic data within the head and neck 5000 study.

Recent, relevant publications (up to 5)

1. Lasseur C, Diergaard B, Olshan AF, Wünsch-Filho V, **Ness AR**, (...) **Thomas S**, (...) Amos CI, McKay JD, Brennan P. Genome-wide association analyses identify new susceptibility loci for oral cavity and pharyngeal cancer. *Nature Genetics* 2016; 48: 1544-50.
2. Schache AG, Powell NG, (...) **Thomas S**, **Ness AR**, **Pring M**, Thomas GJ, King EV, McCance DJ, James JA, Moran M, Sloan P, Shaw RJ, Evans M, Jones TM. HPV-Related Oropharynx Cancer in the United Kingdom: An Evolution in the Understanding of Disease Etiology. *Cancer Research* 2016; 76: 6598-6606.
3. **Ness AR**, Waylen A, Hurley K, Jeffreys M, Penfold C, **Pring M**, Leary S, Allmark C, Toms S, Ring S, Peters TJ, Hollingworth W, Worthington H, Nutting C, Fisher S, Rogers SN, **Thomas SJ**; Head and Neck 5000 Study Team. Recruitment, response rates and characteristics of 5511 people enrolled in a prospective clinical cohort study: head and neck 5000. *Clinical Otolaryngology* 2016; 41: 804-809.
4. Penfold CM, **Thomas SJ**, Waylen A, **Ness AR**. Change in alcohol and tobacco consumption after a diagnosis of head and neck cancer: Findings from Head and Neck 5000. *Head Neck* 2018 [Epub ahead of print].
5. **Dudding T**, Johansson M, **Thomas SJ**, Brennan P, Martin RM, **Timpson NJ**. Assessing the causal association between 25-hydroxyvitamin D and the risk of oral and oropharyngeal cancer using Mendelian randomization. *International Journal of Cancer* 2018 [Epub ahead of print].

Relevant projects (national, EU and others, up to 5)

1. Martin R, Relton C, Brennan P, Davey Smith G, Donovan J, Gaunt T, Higgins J, Holly J, Jeffreys M, Johansson M, Lane A, Lewis S, Muir K, **Ness A**, Perks C, **Timpson NJ**. Reducing the burden of cancer: causal risk factors, mechanistic targets and predictive biomarkers. Cancer Research UK Population Research Committee - Program Award. C18281/A19169. £4,154,270 from 1st June 2015 for five years.
2. Iredale J, Angelini G, Blazeby J, Davey Smith G, Gunnell D, Lawlor D, **Ness A**, Sterne J, Wynick D. NIHR

- Biomedical Research Centre Bristol. £20,858,545 from 1st April 2017 for 5 years.
3. Brennan P, Diergaard B, Hayes DN, Anantharaman D, McKay JD, Tommasino M, Lin Y, Olshan A, Waterboer T, Pawlita M, Hung RJ, Liu G, Ness AR, Relton C, Tajara EH, Boccia S. US National Institutes of Health. The role of germline and somatic DNA mutations in oral and oropharyngeal cancers. \$2,919,204 from 1st February 2019 for 5 years.
 4. Ness AR. NIHR Senior Investigator Award £75,000 from 1st April 2014 for five years.
 5. Dudding T, Thomas SJ, Brennan P, Timpson NJ, Martin R. Vitamin D and head and neck cancer risk and progression: An examination of causality and mechanisms. Wellcome Trust Research Training Fellowship. 201237/Z/16/Z. £187,327 from 01st September 2016 for 3 years.

Infrastructure and facilities available (e.g. equipment, etc)

Head and Neck 5000

WorkPackages 5 and 6 will use data and samples collected in the large UK wide prospective clinical cohort study of people with head and neck cancer (head and neck 5000) which recruited 5,511 people. The study collected socio-demographic data from participants and abstracted clinical information from the notes. Blood samples were obtained on over 4,000 participants (and DNA has been extracted) and formalin fixed tissue blocks are available for over 2,500 participants.

Bristol Bioresource Laboratories

The Bristol Bioresource Laboratories (BBL) provides a biological sample processing and storage service, genotyping and functional assay support to the MRC IEU and to population health scientists across the UK. The BBL have an international reputation for excellence in this area built through experience gained curating the bioresources associated with several flagship cohort studies including ALSPAC and the Head and Neck 5000 cohorts. Since sample governance and a large proportion of sample analysis is carried out in-house, storing samples on-site is a cost effective alternative to off-site storage with the associated distribution costs.

Advanced computing and data storage

Centralized high-performance computing is centered on the UBRIS Advanced Computing Research Centre (ACRC) with a total of £15 million investment in computing and storage. The newest computing cluster (phase 4) provides 15680. In addition to shared access to the main cluster, the MRC-IEU has procured a dedicated sub-cluster of 1232 cores to support large-scale genome-wide association studies. Data storage is provided by 60TB of highly redundant networked disk storage (dual-site mirror with secondary tape backup) provided by the ACRC Research Data Storage Facility, a petabyte-scale facility. In addition, the MRC-IEU have procured 250TB of dedicated scratch storage (with high-speed SSD cache) attached to our dedicated HPC cluster.

Participant 9.**A.C. Camargo Cancer Center (AC-CCC)****Brazil****Description of participating institute**

A.C. Camargo Cancer Center (AC-CCC) has a 65-year distinguished history of fighting against cancer. A leader in scientific knowledge in oncology, the Institution is an international reference center for education, research, and multidisciplinary treatment. The Institution, a private non-profit organization, was established with the pioneering work of Prof. Antônio Prudente and his wife, the journalist Carmen Prudente, who made relentless efforts to revolutionize cancer treatment and research in Brazil.

The Institution offers to its patients a medical practice sustained by scientific knowledge that strives for the integration of its four pillars:

- Diagnostic – Identification of risk factors, diagnosis, secondary and tertiary prevention. Promotion of early disease detection by campaigns focused on prevention and healthy habits, promotion of knowledge, and tracking of main cancer incidences.
- Treatment – Multidisciplinary assistance with integrated, specialized, and coordinated treatment, based on institutional protocols guided by state-of-art scientific knowledge.
- Research – Scientific research projects, ranging from basic to translational and clinical research.
- Education – Continuous development of professionals through residency programs, specialization training, and graduate courses.

Research expertise and research environment

For its first 30 years, research activities at AC-CCC focused mainly on clinical, surgical, and epidemiological studies. In 1983, the Institution established a partnership with the LICR, currently named “Ludwig Cancer Research,” under the leadership of Prof. Ricardo Brentani. This partnership initiated a new era in basic and translational research within the Institution. From 1983 to 2010, Prof. Ricardo Brentani led the LICR Branch in São Paulo and, in 1990, he was invited to take over as Chairman and Director of A.C. Camargo Cancer Center. These strategic positions in both institutions allowed him to promote very influential and fruitful cancer research at A.C. Camargo. The most important programs in scientific research at A.C. Camargo were co-sponsored by the LICR and the FAPESP. Approximately 30 laboratories (including A.C. Camargo’s laboratory) in the State of São Paulo were involved in the Organization for Nucleotide Sequence and Analysis – The Virtual Genomics Institute (ONSA) Network in 1997 and The Human Cancer Genome Project in 1999. The activities of the ONSA Network led to the first genome sequencing of a plant pathogen, *Xylella fastidiosa* (Simpson et al., “The genome sequence of the plant pathogen *Xylella fastidiosa*”, *Nature*, v. 406, pp. 151-157, 2000). The Project generated about 700,000 open reading frame expressed sequence tags from 24 human tissues and represented the second most relevant contribution of The Human Cancer Genome Project Consortia (Camargo, AA, The contribution of 700,000 ORF sequence tags to the definition of the human transcriptome. *Proc Natl AcadSci USA*. 2001 Oct 9;98(21):12103-8). Remarkably, during the period between the two projects, the Institution articulated and organized a cancer tissue biobank. Since then, this biobank (comprised of tissue and macromolecular banks) has amassed more than 60,000 samples (frozen tissue, leukocytes, and plasma) and has become the most important resource for institutional research. A.C. Camargo also coordinated two large long-term national and international cooperative projects supported by the FAPESP and the CNPq: the CEPID (<http://www.bv.fapesp.br/en/8/research-innovation-and-dissemination-centers-ridcs-11-year-grants/>) and (<http://www.bv.fapesp.br/en/174/cnpq-national-institutes-of-science-and-technology-incts>) from 2000 to 2011 and the INCITO (<http://www.bv.fapesp.br/en/auxilios/29217/antonio-prudente-cancer-research-center/>) from 2009 to 2015.

In 2008, the partnership between the LICR and A.C. Camargo was terminated; in 2010, A.C. Camargo launched its own research center, named Centro Internacional de Pesquisa (International Research Center, CIPE for the acronym in Portuguese). According to the Scimago ranking (Scopus), AC-CCC ranks at the 3rd among Brazilian Hospitals. The first- and second-ranked hospitals in Brazil are affiliated with two of the country’s largest public universities (University of São Paulo and Federal University of Rio Grande do Sul, Porto Alegre). Other than Barretos Cancer Hospital, however, all hospitals listed in Brazilian Ranking are general hospitals (thus, not dedicated exclusively to cancer treatment and research).

The number of articles published annually by the Institution remained constant from 2013 to 2017 (160, 167, 168, 183, and 182 respectively).

Overview of research activities

The strategic research areas were chosen according to maturity and development levels in clinical and translational research (hereditary cancer syndromes, head and neck tumors) and in areas in which the Institution has a greater capacity to produce relevant and competitive scientific knowledge (kidney tumors, gastric cancer, Head and Neck tumors, sarcomas and rare tumors). The areas related bellows are aligned with our main research strategic plan.

- Hereditary Cancer Syndromes

The study of hereditary cancer syndromes is one of the most established research areas of A.C. Camargo. This field has been under intense investigation since 2000 and the expertise of the clinical and scientific staff, has placed the Institution as one of the main oncogenetics and oncogenomics leaders in South America, with large hereditary cancer syndrome patient cohorts, especially Li-Fraumeni syndrome.

Genetic susceptibility plays a crucial role in the etiology of a significant proportion of all cancers, and subjects carrying mutations that predispose to cancer development require special and long-term attention. Therefore, germline mutation testing for inherited predisposition of cancer is part of the standard of care for members of families with a hereditary cancer syndrome (HCS). In the last 10 years, A.C. Camargo has supported multidisciplinary efforts that were essential to improve the clinical and genetic assessment of HCS-subjects. The results of all these efforts are reflected in the significant improvement of clinical management for those who carry pathogenic mutations, based in reinforced surveillance and prevention. To date, more than 1,500 patients with clinical features for HCS were screened for pathogenic variants in genes associated with the main HCSs. However, the finding that only about 25% of the patients tested positive for the screened mutations is a major motivation for a continuous effort to identify causative mutations in a slew of patients.

- Head and Neck tumors

Head and neck squamous cell carcinomas (HNSCC) comprise a heterogeneous group of tumors that differ, not only as a function of anatomic site, but also with respect to risk factors, pathogenesis and clinical behavior. Among HNSCC, oral and oropharyngeal squamous cell carcinoma represent a major concern, due to high mortality rates and increasing incidence, especially of HPV-related SCC in young patients. In the last decades, improvements in survival rates were reported for nasopharynx and oropharynx tumors, but remained unchanged for oral cavity and were associated with an alarming decrease in survival for laryngeal cancers¹⁰. Approximately 43% of patients present lymph node metastasis at the diagnosis, and 10% already have distant metastasis.

In many cases, the therapies available are clearly deficient. For early-stage disease, surgery or radiotherapy generally offers high rates of tumor control and survival. However, for advanced tumors, even the combination of chemotherapy, radiotherapy and surgery, still poses a significantly worse prognosis. Therefore, it is essential to develop prognostic markers and to discover better therapeutic modalities capable of improving survival and quality of life.

- Kidney tumors

Renal cell Carcinomas Research on kidney cancer has been a priority at A.C. Camargo since 2014, when the Latin American Renal Cancer Group (LARCG) initiative was established, led by the Urology and Pathology departments. The LARCG is composed of members from 44 institutions in 8 countries, with thousands of cases reviewed and reclassified by specialized pathologists and precise clinical information collected from about 6,000 patients. This large collection of tumor samples and data will allow the Institution to lead epidemiological, clinical, and basic/translational studies.

Renal cell carcinoma (RCC), the most common form of kidney cancer, includes a heterogeneous group of cancers with different genetic and molecular alterations. The most common histologic subtype is clear-cell carcinoma, characterized by the disruption (by loss of heterozygosity (LOH) of chromosome 3p, mutation or methylation) of the tumor suppressor von Hippel Lindau (VHL), mutations in PI(3)K/AKT, chromatin remodeling pathways and alterations of cellular metabolism. Less common RCC subtypes include papillary (types 1 and 2), and chromophobe carcinoma, each of which have been associated with unique molecular profile. These groups still need better characterization on epidemiological, clinical, and genetic aspects.

At initial clinical presentation, approximately 30% of patients RCC already have metastatic disease, 20% have locally advanced disease. Whereas the main treatment for stages I to III is surgical resection, up to 30% of patients diagnosed with a disease that appears to be restricted to the kidney, will relapse to metastatic disease. The therapeutic landscape for metastatic disease has evolved considerably with active therapies directed against angiogenesis, mTOR pathways and PD-1/PD-L1 blockage. However, targeted therapies often fail and tumors develop resistance (acquired vs. de novo resistance). Complete remission in advanced cases is a rare event and in most cases the “switching drugs” method is adopted.

- Gastric tumors

Gastric adenocarcinomas (GACs) have relevant prevalence and mortality in Brazil. An interesting aspect of this malignancy is the reported discrepancy of prognosis and response to therapy, which appears to be related to ethnicity; for example, contrarily to western populations, Asiatic GAC-patients have been shown not to benefit from anti-angiogenic therapeutics but usually have better overall and disease-free survival rates. As Brazil has a considerable ethnical admixture, we have great interest in the study of the genomic aspects of GACs. The Genomics and Epidemiology for Gastric Adeno Carcinomas (GE4GAC) consortium, coordinated by AC-CCC, aims to perform a detailed epidemiologic and experimental evaluation of GAC in Brazil, including microbiome studies, familial and early onset GACs, resistance to perioperative chemotherapy and prognostic factors.

- Soft-tissue sarcomas

Soft-tissue sarcomas (STS) are tumors derived from mesenchymal tissue and represent 1% of all malignancies, more than 10% of pediatric solid malignancies, and 8% of solid malignancies in adolescents and young adults. Most cases develop in the extremities of the limbs, but they can also be present in the chest wall, head and neck area and retroperitoneum. The etiology of sarcomas is unknown, but an increased risk was correlated with early age radiotherapy treatment or human herpesvirus-8 infection (Kaposi's sarcoma). These tumors usually develop lung metastatic disease, high rates of morbidity and mortality. The treatment options still limited with low rates of response and survival. Morphological classification of sarcomas based only in histogenesis has a questionable prognostic value, with several tumors with unknown cell differentiation. Histological grade still very useful clinically, and it takes into accounts histological differentiation, mitotic index and necrosis. Based on molecular characteristics, STSs can be divided in two groups: one showing karyotypic disorganization and the other carrying specific chromosomal alterations and fusion events. The latter group, more prevalent in young subjects, may present better possibilities for target therapy development²⁰. The mechanisms of sarcogenesis are elusive and transition among different mesenchymal phenotypes is frequent, suggesting different types of reprogramming and dedifferentiation processes in these tumor cells. The genetic basis of sarcomas suggests that most cases could be affected by germline mutations, being associated to familial aggregation cancers a condition characterized by contribution of multiple inherited genes and environmental factors in the development of malignant disease. AC-CCC is a reference center for sarcoma treatment in Brazil, with about 1,800 cases diagnosed and treated since 2007.

- Rare tumors

Rare tumors are defined as those with an incidence of fewer than 5 or 6 cases per 100,000 persons per year²². Research on rare tumors offers a unique leadership opportunity for AC-CCC, as a reference cancer center in Brazil and South America. These tumors, which together represent 22–25% of all cancers, have worse prognoses than do more commonly occurring tumors, due mainly to limited knowledge of their biology and the overall unavailability of patients for clinical trials. There is a lack of concerted efforts in Brazil to biobank rare tumors and to structure study groups, which results in a scarcity of treatment options and a blurred picture of the impact of these diseases in our society. Series of rare tumors have been identified in AC-CCC's tumor bank and historical collection of formalin-fixed and paraffin-embedded (FFPE) tissue blocks is available. The organization of collaborative groups similar to the LARCG will offer valuable opportunities to improve the understanding of some of these diseases and, hopefully, organize clinical trials for these patients.

Role in the proposal and relevant infrastructure

AC-CCC will develop the communication strategy for HEADSpAcE (WP8 Dissemination), along with UGLA (Partner 6). It will also use its recognized clinical expertise in head and neck cancers to evaluate and develop national and international treatment protocols and guidelines.

The Nucleus of Epidemiology and Statistics (NEE) of AC Camargo Cancer Center has a team of statistician, epidemiologist, project manager able to perform data quality evaluation and epidemiological analysis using advanced statistical methods.

The team has experience in cohort and case-control studies and support young researchers and translational and basic research on cancer.

The NEE will be responsible to retrieve information about the role of lifestyle, comorbidities, SES, infectious, clinical and genomic characteristics on survival after HNC diagnosis. Additionally, to identify the current guidelines adopted for treatment in South America and Europe.

Role of key scientific people

Dr Maria Paula Curado (female)

I am the heading the Nucleus of Epidemiology and Statistics (NEE) at International Research Center (CIPE), AC Camargo Cancer Center in Sao Paulo/Brazil. My main my activities are to analyses lifestyle risk factors and survival outcomes for head and neck cancer, gastric cancer, etc. In HEADSpAcE project my group is going extract and analyses lifestyle risk factors of patients from InterCHANGE and to investigate the existence of comorbidities pre and post treatment and its outcomes and survival of these patients. In collaboration with my colleague surgeon LP Kowalski (Head of Head and Neck surgery group of AC Camargo Cancer Center) were are going to identify the treatments adopted in South America for oral cavity, oropharynx and larynx. Based on the medical records we plan to implement a guideline taking in to account clinical, pathological stage, and treatment planned of these patients, aiming to understand the gaps and the differences and outcomes such abandon of treatment and, palliative care, etc.

To strength our sample we are going to recruit 200 new HNC cancer cases in Sao Paulo to investigate co morbidities (pre and post treatment), sexual habits, treatment plans and survival (recurrence, metastasis and death) outcomes in the first, second, third year after treatment.

Dr Luiz Paulo Kowalski (male)

I am head neck surgeon leading the Head and Neck nucleus at AC Camargo Cancer Center. This is the major group of head and neck cancer treatment in Sao Paulo. During my career I had been promoting research in head and neck cancer in the clinical and surgical settings associating with molecular biomarkers looking toward to identify and implement better treatment plans. Within this project I intend to better understand the treatment planned for HNC patients of South America comparing the outcomes with European countries looking to implement more accessible treatment through and adapted guidelines for this region.

Recent, relevant publications

1. Rodrigo JP, Grilli G, (...) **Kowalski LP**, Suárez C, López F, Quer M, Boedeker CC, de Bree R, Coskun H, Rinaldo A, Silver CE, Ferlito A. Selective neck dissection in surgically treated head and neck squamous cell carcinoma patients with a clinically positive neck: Systematic review. *Eur J Surg Oncol*. 2018 Apr;44(4):395-403
2. Lira RB, de Carvalho AY, de Carvalho GB, Lewis CM, Weber RS, **Kowalski LP**. Quality assessment in head and neck oncologic surgery in a Brazilian cancer center compared with MD Anderson Cancer Center benchmarks. *Head Neck*. 2016 Jul;38(7):1002-7
3. Amit M, Yen TC, Liao CT, Chaturvedi P, Agarwal JP, **Kowalski LP**, (...) Shah JP, Patel SG, Gil Z. Prognostic Performance of Current Stage III Oral Cancer Patients After Curative Intent Resection: Evidence to Support a Revision of the American Joint Committee on Cancer Staging System. *Ann Surg Oncol*. 2015 Dec;22 Suppl 3:S985-91
4. Hashim D, Sartori S, Brennan P, **Curado MP**, (...) Hashibe M, Vecchia CL, Boffetta P. The role of oral hygiene in head and neck cancer: results from International Head and Neck Cancer Epidemiology (INHANCE) consortium. *Ann Oncol*. 2016 Aug;27(8):1619-25
5. Berthiller J, Straif K, Agudo A, Ahrens W, Bezerra Dos Santos A, Boccia S, Cadoni G, Canova C, Castellsague X, Chen C, Conway D, **Curado MP**, (...) Brennan P, Boffetta P, Hashibe M, Lee YC. Low frequency of cigarette smoking and the risk of head and neck cancer in the INHANCE consortium pooled analysis. *Int J Epidemiol*. 2016 Jun;45(3):835-45

Relevant projects

1. FAPESP: N° 2009/57887-9 - INCITOFAPESP - Instituto Nacional De Oncogenômica - R\$ 2.563.107,57
2. FAPESP: N° 2008/00733-0 - Historia Natural Das Lesoes Precursoras Do Cancer Oral E Orofaringeo R\$ 154.994,70
3. CNPQ: N° 573589/2008-9 – INCITO CNPQ - Instituto Nacional De Oncogenômica - R\$ 2.277.278,45
4. CNPQ: N° 454655/2014-2 - Marcadoresepigenticos Em Carcinomas Epidermoides Orais E De Orofaringe - R\$ 90.000,00
5. Ministério da Saúde: Ministry of Health: Estudo Epidemiológico E Molecular Da História Natural Do Cancer Da Cavidade Oral: Base Para Prevenção E Tratamento - R\$ 3.872.386,75

Infrastructure and facilities available for HEADSpAcE

Established in August 2010, the Centro Internacional de Pesquisa (International Research Center, CIPE) at A.C.Camargo Cancer Center has an area of 4,000 m² spread over nine floors (five of which are currently occupied), with two large laboratories currently used by more than 120 persons, including professionals and students, dedicated to research in the areas of epidemiology and statistics, genomics, tumor biology and biomarkers, investigative pathology, and bioinformatics. The infrastructure for research is distributed over five floors. It includes an animal facility (basement); microscopy and flow cytometry facilities, and National Biosafety level 1 (NB-1) and NB-2 rooms dedicated to cell culture (ground floor); and facilities for microarray research, next-generation sequencing, nucleic acid extraction, polymerase chain reaction (PCR), gel electrophoresis, immunohistochemistry, and medical informatics research (first floor). An administrative area and a conference room are located on the second floor. The Nucleus of Epidemiology and Statistics in Cancer and Clinical Trials off cells are located on the third floor (Fig. 1).

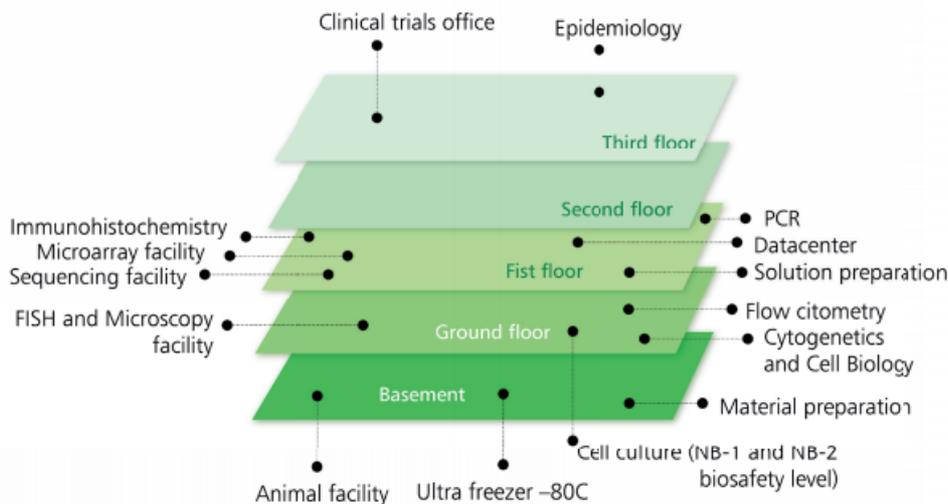


Figure 1 - CIPE infrastructure: dedicated rooms

The animal facility, with an area of more than 300 m², is dedicated to the maintenance of and experimentation on immunodeficient and transgenic mice. It is equipped with an in vivo Bruker FX Pro system. The area includes three specialized rooms for animal breeding, experimentation, and surgery. The CIPE has a complete infrastructure for DNA and RNA processing, sequencing, and analysis. Currently, the next-generation sequencing facility has three high-performance sequencing platforms, with one Ion PGM Torrent, two Ion Proton, one NextSeq 500, and 454 GS Junior systems. PCR steps, the construction of libraries for sequencing platforms, and genomic fragmentation are conducted with available accessories, including three OneTouch 2, two OneTouch Enrichment, Covaris, and S2 Hydroshea devices.

Dedicated computing resources and a data center with 18 servers, 180 cores, 504 GB RAM, and 110 TB storage are located in the Institution to support scientific research and management activities. Server administration is performed by a specialized team and supervised by the Medical Informatics Laboratory. The Project Management office offers administrative and technical support for research projects. A set of specialized informatics tools developed in house enables project management, access to anonymized medical records, and sample requests. Among them are Biobank, which enables management of the use of all tumor and biopsy tissues and their respective clinical data; H²TC, an integrated system of medical records with a research focus; Recruit, which facilitates the identification of patients by clinical criteria; XUSD, which enables the construction and sharing of research databases; and acProjects, for the management of scientific projects, which ensures that only participants approved by the Ethics Committee have access to anonymized patient data.

AC-CCC's biobank was created in 1997 and, together with the macromolecule bank, created in 2004, stores tissue samples and centralizes macromolecule purification from all human samples collected with patients' informed consent. This facility is localized at AC-CCC main campus and is equipped with a QIASymphony SP workstation for automated purification of DNA, RNA, and proteins, as well as cryopreservation freezers. When a tissue sample is requested from the biobank, the RNA and DNA are extracted following standard protocols, and an aliquot of the macromolecule of interest is provided to the investigator. The remaining parts of the macromolecule are stored

according to technical standards for tumor biobanks recommended by the World Health Organization's International Agency for Research on Cancer (IARC). The decision to centralize the extraction and distribution of macromolecules was based on the need to implement quality control checks to ensure the high quality of nucleic acid samples.

To date, more than 70,000 samples have been collected. Of these, 42,933 are tissue (tumor and normal) and 20,171 are whole blood samples. At the end of 2015, 33,117 tissue samples (tumor, normal adjacent tissues, and metastases) were stored. From 2010 to 2015, a total of 145 projects were conducted using samples from the biobank. The macromolecule bank processed approximately 20,000 RNA and DNA extractions. Integrated with the CIPE, the Investigative and Molecular Pathology Group employs state-of-the-art diagnostic techniques and is dedicated to understanding the predictive and prognostic behaviors of different types of cancer. Its infrastructure includes facilities for immunohistochemistry, PCR, microarray (cDNA and Tumor Microarrays, TMA), pyrosequencing, DNA sequencing, chromogenic and fluorescent in situ hybridization, laser microdissection, and gene rearrangement studies, among other molecular techniques.

Participant 10.**Barretos Cancer Hospital (HCB)****Brazil****Description of participating institute****Research expertise and research environment**

The Barretos Cancer Hospital (HCB), a non-profit foundation, is a national reference in cancer treatment that receives patients from more than 1,300 cities, with an average of 4,000 appointments per day and 11,000 new cancer patients per year, all at no cost for the patients. Besides treatment, other notorious activities of the hospital are cancer prevention programs and basic, clinical and translational cancer research.

The Molecular Oncology Research Center is the research unit of the Teaching and Research Institute at HCB and one of the most comprehensive cancer research centers in Brazil, with modern equipment and infra-structure. It is a center for knowledge generation, training of students and professional qualification in the country, enabling the strengthening of partnerships with the main national and international research centers.

Overview of research activities

The Molecular Oncology Research Center (led by Rui Reis) includes several lines of research directed to specific tumor groups (pediatric, hereditary, head and neck, melanoma) or focused on specific features of basic research (Cancer Biology and Therapy, Cancer epigenetics, Cancer Genomics).

The main objectives of the Molecular Oncology Research Center are expanding and supporting molecular research in cancer, through molecular epidemiology, translational and pre-clinics studies aimed at the knowledge of the basis of tumor development and progression, the identification of cancer biomarkers for risk, diagnosis, prognosis and therapy response as well as new therapy targets. The center participates in many international consortiums such as The Cancer Genome Atlas (TCGA), International Cancer Genome Consortium (ICGC) among others.

Role in the proposal and relevant infrastructure

Besides contributing in the experimental design and decision-making throughout the project, HCB is going to participate in WP7 by providing expertise, tissue and plasma samples to validate the cancer gene-panel detection in body fluids and will also participate in the validation step of epigenetic markers in WP5. The institution has a lot of experience and a complete infra-structure for collection, processing and storage of biological samples (tissue and fluids) in one of the largest biorepositories in the county and the equipment needed for these tasks. It also has a department that supports researchers and coordinates several phases of the projects from development, grant submissions, data collection and analysis. Moreover, HCB's Department of Information Technology (IT) provides deployment and integration support for research data management using the REDCap (Research Electronic Data Capture) application, allowing researchers to create projects with data collection instruments and share those projects with colleagues. Therefore, the institution provides full support and infrastructure for the development of this project.

Role of key scientific people**Dr Ana Carolina de Carvalho (female)**

Dr de Carvalho has a strong background in the study of gene expression-modulating alterations during cancer initiation and progression in the genetic, non-coding RNA and epigenetic levels. As a post-graduation student at Federal University of São Paulo she was involved in several studies aimed at identifying specific molecular traits in different types of samples collected from cancer patients such as: fresh and FFPE tissue, blood, plasma, oral rinse and saliva, through different techniques. Currently, she is a Professor and a Researcher at HCB where she participates in several studies aimed to understand the risk factors associated and the molecular traits behind the initiation and progression of tumors, in order to enable a better characterization of these patients according to their outcome and treatment response profiles, therefore offering more efficient prevention strategies and a more personalized management of the disease. She has several publications in the field of aberrant DNA methylation through the quantitative analysis of DNA methylation using quantitative methylation-specific PCR and bisulfite pyrosequencing. Therefore, with the experience she has in epigenetic studies, hence, gene-methylation profiles in different types of tumors and large number of samples from different sources, she is well qualified to be part of the team of collaborators in this project.

Dr André Lopes Carvalho (male)

Dr Lopes Carvalho is a Professor and Researcher at the Teaching and Research Institute (Barretos Cancer Hospital), and a Visiting Scientist at Fred Hutchinson Cancer Research Center (Seattle, US). He has been trained as a head and neck surgeon, has a Ph.D. in Oncology (clinical research track) and an MPH. Dr Carvalho's primary area of work is clinical and molecular epidemiology of head and neck cancers. He has been involved in many national and international consortiums and participates in collaborative studies, leading clinical trials, cohort and case-control studies in the field. Regarding translational research, the main focus is understanding the carcinogenesis and the search for biomarkers for diagnosis, prognosis, and surveillance (mainly epigenetics) of head and neck cancers. He has co-authored over 175 publications in peer-review scientific journals.

Dr Rui M. Reis (male)

Dr Reis implemented and is the Coordinator of the Molecular Oncology Research Center, and Molecular Diagnostic Laboratory of Barretos Cancer Hospital, Brazil, and Assistant Professor of Medicine School, and Principal Investigator at ICVS, Minho University, Portugal. Dr Reis performed his PhD on neuro-oncology at IARC, France, and a post-doc on cancer genomics at VUMC, The Netherlands and IPATIMUP, Portugal. His research interests are on molecular pathology, cancer cell biology, and cancer biomarkers. Dr Reis, is a steering member of ICGC and WIN consortiums, and published more than 140 articles in international journals and earned several scientific awards.

Recent, relevant publications

1. Pereira CM, **de Carvalho AC**, da Silva FR, Eliseo MM, Lessa RC, Andrade VCC, Kowalski LP, Vettore AL, **Carvalho AL**. In vitro and in silico validation of CA3 and FHL1 downregulation in oral cancer. *BMC Cancer*. 2018 Feb 17;18(1):193
2. Arantes LM, **de Carvalho AC**, Melendez ME, **Carvalho AL**. Serum, plasma and saliva biomarkers for head and neck cancer. *Expert Rev Mol Diagn*. 2018 Jan;18(1):85-112
3. Arantes LM, **de Carvalho AC**, Melendez ME, Centrone CC, Góis-Filho JF, Toporcov TN, Caly DN, Tajara EH, Goloni-Bertollo EM, **Carvalho AL**; GENCAPO. Validation of methylation markers for diagnosis of oral cavity cancer. *Eur J Cancer*. 2015 Mar;51(5):632-41
4. Rettori MM, **de Carvalho AC**, Longo AL, de Oliveira CZ, Kowalski LP, **Carvalho AL**, Vettore AL. TIMP3 and CCNA1 hypermethylation in HNSCC is associated with an increased incidence of second primary tumors. *J Transl Med*. 2013 Dec 20;11:316
5. Rettori MM, **de Carvalho AC**, Bomfim Longo AL, de Oliveira CZ, Kowalski LP, **Carvalho AL**, Vettore AL. Prognostic significance of TIMP3 hypermethylation in post-treatment salivary rinse from head and neck squamous cell carcinoma patients. *Carcinogenesis*. 2013 Jan;34(1):20-7

Relevant projects

1. Randomized, phase 3 clinical trial on induction chemotherapy followed by chemoradiation vs. chemoradiation for advance clinical stage HNC. Funding: National Council for Scientific and Technological Development (CNPq). Andre Lopes Carvalho (PI) Value: ~400,000 USD
2. Comparison of the methylation profile of specific genes between HPV -positive and HPV- negative head and neck squamous cell carcinomas. Funding: National Council for Scientific and Technological Development (CNPq) - Ana Carolina de Carvalho (PI) Value: ~10,000 USD
3. Characterization of genetic and epigenetic alterations in specific genes in HPV-positive and HPV-negative tumors of patients with Head and Neck Squamous Cell Carcinoma. Funding: São Paulo Research Foundation (Fapesp) - 01/11/15-04/30/18 André Lopes Carvalho (PI), Ana Carolina de Carvalho (co-PI). Value: ~70,000 USD
4. Head and Neck Oncology Translational Research. Funding: National Council for Scientific and Technological Development (CNPq). Andre Lopes Carvalho (PI) Value: ~38,000 USD
5. Barretos Cancer Hospital participation on The Cancer Genome Atlas (TCGA) Research Network. Andre Lopes Carvalho (TSS - Site Principal Investigator). Funding: National Cancer Institute (NCI - USA). Value: ~400,000 USD

Infrastructure and facilities available for HEADSpAcE

HCB is equipped with modern equipment for research in molecular biology including: Nanostring Platform (Ncounter) for direct multiplexed measurement of analytes; Ion Torrent (Life Technologies/ Applied Biosystems) and MySeq (Illumina) for NGS; QX200 Droplet Digital PCR System (Biorad) and QuantStudio 3D Digital PCR 825771 HEADSpAcE – Part B

(Life Technologies) for digital PCR; Microarray Agilent (GE healthcare) for expression arrays; Varioskan Flash Reader (Thermo Scientific) for spectral reading; the pyrosequencer Pyromark Q96 ID (Qiagen) for target sequencing; and several qPCR equipment (Applied Biosystems 7900HT Fast Real-Time PCR system; QuantStudio 6 Flex Real-Time PCR System; StepOne Real-Time PCR System) among others.

Participant 11.**Hospital Santa Rita De Cássia (AFECC)****Brazil****Description of participating institute****Research expertise and research environment**

The Hospital Santa Rita de Cássia (AFECC) is a philanthropic entity recognized throughout the State as a reference in the treatment of cancer. Currently Hospital Santa Rita has about 1,500 employees and more than 400 doctors in the clinical body dedicated to the health and well-being of the cancer patients with about 755,000 visits to patient by year. Together with the Molecular Pathology Laboratory, based at Federal University of Espírito Santo, they form the regional reference center for multidisciplinary care to cancer patients and research in oncology.

The Head and Neck Division of the AFECC, in collaboration with the Molecular Pathology Lab, focuses on head and neck cancer research and on the education of health professionals in the field. There are three main themes of research: translational and molecular medicine, clinical effectiveness and quality of life and functional outcomes. Molecular medicine involves the understanding of how diseases develop within the cell at a molecule level within those cells. Translational medicine then takes the new understanding of disease and develops further to a point where new treatments can be used in patients within clinical practice. Within this theme our group is focused on Biomarkers and risk stratification assessment and its correlation with functional outcomes. Research in the Clinical Effectiveness and Quality of life fields look at how well current and new treatments work, and how effective diagnostic tests are when used in clinical practice. The areas of research in this theme include incorporating quality of life assessment in routine clinical practice.

Overview of research activities

The interdisciplinary and innovative investigations at AFECC improve the benefits for patient care practices in the cancer treatment. The Head and Neck team, in collaboration with the Pathology team, focus on basic-translational research, which aims to transfer scientific knowledge to clinical and patient's bed. The work is developed in collaboration with the clinical and patient care staff and is carried out in laboratories with equipment for studying cellular and molecular biology.

The core activity of our group of scientists is to study tumor tissues, cells, molecules and virus, in order to understand the mechanisms and pathways by which tumors develop, grow and disseminate (metastases), identifying potential targets for therapy, biomarkers for diagnosis, prognosis and response to treatment. In addition, our team works to transfer the knowledge acquired in basic research to clinical practice. It consists of applying the molecular knowledge of the mechanisms related to the tumor process, in combination with studies involving patients or their biological material, in order to understand and, as a result, to solve challenges in the daily clinical activities. To develop research in this field we work with different techniques to assess gene expression being the most used the reverse transcription polymerase chain reaction quantitative real time (qRT-PCR), *in situ* Hybridization using DNA/RNA probes and immunohistochemistry. In the field of diagnostic, our core activity is to identify HPV E6/E7 mRNA in tumor tissues from patients with Head and Neck Cancer. All data obtained from these assays are correlated with clinical outcomes and treatment response in clinical practice.

Role in the proposal and relevant infrastructure

The main role of AFECC in the current proposal is to participate in WP3 to assess performance characteristics of routine biomarkers for identification of HPV-driven oropharyngeal cancer (OPC) in the routine clinical setting: HPV DNA and p16 IHC. In this step, the core activity is to validate a novel diagnostic RNA-based chromogenic *in situ* hybridization (ISH) technique (RNAscope) capable of reliably detecting transcriptionally active genes, including HR-HPV E6/E7 oncogenes, in FFPE tissue from OPC, and to compare assay performance to routine clinical methods. In addition, we will help to comprehensive describe immunohistochemical characteristics of HPV driven vs non-HPV driven oropharyngeal cancers.

In addition, the AFECC is contributing in the experimental design and decision-making throughout the project, and is going to participate in WP2 by providing biological samples and clinical data to assess the socio-economic, logistic and biological predictors of late stage at diagnosis.

Role of key scientific people

Dr José Roberto Vasconcelos de Podestá (male)

Dr Podesta is a Head and Neck surgeon at AFECC. He has been trained as a head and neck surgeon at Instituto Nacional do Câncer (INCA, Rio de Janeiro – Brazil). He will lead the head and neck clinical team for select cancer patients and coordinates the follow-ups. He is the PI in the InterCHANGE Study coordinate by IARC.

Dr Sandra Ventorin von Zeidler (female)

Dr von Zeidler is a Pathologist, and has PhD at Oral Medicine and Oral Pathology at Universidade de São Paulo and Post-doctoral internship at School of Cancer Sciences - University of Birmingham, United Kingdom. Has experience in Oncology, acting on the following subjects: oral cancer and molecular biomarkers of Head and Neck tumors. Currently she is a Professor at Federal University of Espírito Santo and Coordinator of the Post-graduate Program in Biotechnology. In this proposal she will lead a team of 8 biologists and pharmacists and coordinates the assays related to RNA-based chromogenic *in situ* hybridization (ISH) technique (RNAscope) capable of reliably detecting transcriptionally active genes, including HR-HPV E6/E7 oncogenes; p16 IHC; HPV DNA and histopathological analysis. She has several publications in the field of head and neck tumors and has experience in the histopathological field and in the techniques cited above. She has been involved in many national and international consortiums and participates in collaborative studies, leading translational and basic research projects in the field of head and neck tumors. Regarding translational research, the main focus is understanding the carcinogenesis and the search for biomarkers for diagnosis, prognosis, and surveillance of head and neck cancers.

Recent, relevant publications

1. Mehanna H, Wong WL, McConkey CC, Rahman JK, Robinson M, Hartley AG, Nutting C, Powell N, Al-Booz H, Robinson M, Junor E, Rizwanullah M, **von Zeidler SV**, Wiesmann H, Hulme C, Smith AF, Hall P, Dunn J; PET-NECK Trial Management Group. PET-CT Surveillance Versus Neck Dissection In Advanced Head And Neck Cancer. *N Engl J Med*. 2016 Apr 14;374(15):1444-54
2. **von Zeidler SV**, de Souza Botelho T, Mendonça EF, Batista AC. E-cadherin as a potential biomarker of malignant transformation in oral leukoplakia: a retrospective cohort study. *BMC Cancer*. 2014 Dec 17;14:972
3. Oliveira KG, **von Zeidler SV**, **Podestá JR**, Sena A, Souza ED, Lenzi J, Bissoli NS, Gouvea SA. Influence of pain severity on the quality of life in patients with head and neck cancer before antineoplastic therapy. *BMC Cancer*. 2014 Jan 24;14:39
4. Oliveira KG, **von Zeidler SV**, Lamas AZ, **Podestá JR**, Sena A, Souza ED, Lenzi J, Lemos EM, Gouvea SA, Bissoli NS. Relationship of inflammatory markers and pain in patients with head and neck cancer prior to anticancer therapy. *Braz J Med Biol Res*. 2014 Jul;47(7):600-4
5. Priscila Marinho Abreu; Pedro Leite Azevedo; Anna Clara Gregório C6; Isabella Bittencourt Do Valle; Karine Gadioli De Oliveira; S6nia Alves Gouvea; Melissa Freitas Cordeiro-Silva; Iuri Drumond Louro; **Jos6 Roberto Vasconcelos De Podest6**; Jeferson Lenzi; Agenor Sena; Elismauro Francisco De Mendonça; **Sandra Ventorin Von Zeidler**. Frequency Of HPV In Oral Cavity Squamous Cell Carcinoma. *BMC Cancer*, 2018. Bcan-D-16-01484r5 (Status: Accepted In Press)

Relevant projects

1. Study of Head and Neck Cancer in South America - InterCHANGE Study. Funding: International Agency for Research on Cancer, France. José Roberto Vasconcelos de Podestá (PI).
2. Improving treatment selection using Predictive Classifiers of Treatment Response for Head and Neck Cancers and dysplasia - PREDICTR-HNC. Developed in collaboration with Institute of Head and Neck studies and Education, University of Birmingham, United Kingdom. Funding: Cancer Research UK. Hisham Mehanna (PI).
3. Oral cancer biomarkers. Developed in collaboration with Federal University of Goias. Sandra von Zeidler (PI). Funding: FAPES
4. Validation of a new technique to diagnose HPV E6/E7 mRNA in oropharyngeal squamous cell carcinoma for clinical practice and its impact as predictor of survival in South American Cancer Centers. Developed in collaboration with A.C. Camargo Cancer Center-SP, Federal University of Goias and Federal University of Espírito Santo. Sandra von Zeidler (PI)
5. Prognostic biomarkers in oral and oropharyngeal squamous cell carcinoma. Funding: FAPES. Sandra von

Zeidler (PI).

Infrastructure and facilities available for HEADSpAcE

All clinical activities, including patient selection and follow-ups will be performed at AFECC.

The assays to investigate biomarkers and detect HPV in head and neck tumors will be performed at Molecular Pathology Laboratory. The Lab is equipped with modern equipment, of which we highlight an Eppendorf refrigerated centrifuge with tube rotors of various sizes, 01 Freezer -80C with generator system with autonomy of 8h; exhaust booth for handling chemical reagents; a pre-PCR room with vertical laminar flow; 1 PCR room with 1 Real-Time PCR System (Applied Biosystems® 7500) and 3 thermocyclers (one from Applied Biosystems 9700, one Eppendorf and one Biorad); microcomputers and laser printers. In addition, we have the necessary infrastructure to perform immunohistochemistry, microscope coupled to photodialing system (Zeiss Axio Cam and Primo Star), Panoramic Viewer image analysis system (version 1.15 3DHISTCH®, Hungary) and in situ hybridization system to perform hybridization with RNA/DNA probes (Hybrid Z system, ACD), among other equipment. In addition, we have all facilities available and technical team to proceed the histopathological analysis.

Participant 12.**University El Bosque (UnBosque)****Colombia****Description of participating institute****Research expertise and research environment**

El Bosque University (UnBosque) is a higher education institution and a private, non-profit organization. The University promotes the creation of scenarios for the development of research activities, focused in health and impact the quality of life in response to trends and needs of the local, national and international community. We work for a culture of scientific, humanistic and artistic research, in order to generate technological and innovative developments, through the activities of institutes and research groups working in the academic units. The University has more than 40 research groups, seventy percent is currently affiliated to the faculty of Medicine and are focused on 3 main areas of research: clinical research, basic health sciences and public health.

Overview of research activities

El Bosque University promotes scientific and technological development supporting the foundation of knowledge, innovation and transfer based on continuous collaborative alliances with institutions of high standards such as Fundación Santa Fe de Bogota University Hospital. El Bosque University within the framework of the Alliance with Fundación Santa Fe de Bogota University Hospital jointly develops the Graduate Program in Medicine, in such a way that supports training and research activities of students of clinical specialties in Internal Medicine, radiology, general surgery and oncology. The Head and Neck cancer group actively participate in comprehensive research projects and holds monthly discussions over clinical management for all patients treated at the institution.

Role in the proposal and relevant infrastructure

El Bosque University will lead WP3. It is currently participating in projects investigating the main genetic determinants, environmental and epidemiological characteristics of prevalent cancers in Colombia and its correlation with the clinical characteristics of the disease. The department of Pathology in Fundación Santafé de Bogotá University Hospital is a reference laboratory in anatomic and clinical pathology. Leader and pioneer in innovation, diagnostic, teaching and research at the national level. It has a broad portfolio of tests, both in pathology and clinical laboratory, and a network of national and international support. The services offered range from routine tests to high standard molecular tests for the comprehensive diagnosis of diseases of different complexities. The particular experience in head and neck pathology makes it a suitable laboratory to perform all the pathology and immunohistochemical assays to be developed in WP3 and the analytical experience and genomic research facilities will be used to complete WP7.

Role of key scientific people**Dr Sandra Perdomo (female)**

Dr Perdomo is a professor at the Faculty of Medicine and leader of the Institute of Nutrition, Genetics and Metabolism Research at El Bosque University. Dr Perdomo has a Bachelor in Science from the George Mason University in Virginia, US and pursued a PhD degree in Cancer Molecular Biology from The University of Salamanca in Spain. Postdoctoral training in epidemiology from Instituto Carlos III in Spain and postdoctoral fellowship in Genetic Epidemiology from IARC. During the last 4 years she has participated as co-coordinator of the InterCHANGE study and developed genetic epidemiology studies on head and neck cancer including integrating genomic analysis and lifestyle exposures and evaluation of non-invasive biomarkers.

Dr Paula Rodríguez (female)

Dr Rodríguez is a Medical Doctor, specialist in Anatomical and Clinical Pathology at Robert Wood Johnson Medical School, with a fellowship in Cytology at Mount Sinai Medical Center and a fellowship in Oncologic Pathology at the Memorial Sloan-Kettering Cancer Center. She is currently the director of the Cytology at the Department of Pathology of the Fundación Santa Fé de Bogotá. She is the principal investigator of the InterCHANGE project in Bogotá and the coordinator of the Head and Neck group in Fundación Santafé de Bogotá.

Recent, relevant publications

1. **Perdomo S**, Anantharaman D, Foll M, Abedi-Ardekani B, Durand G, Reis Rosa LA, Reetta Holmila, Florence LeCalvez-Kelm, Eloiza H. Tajara, Victor Wunsch-Filho, Jose Eduardo Levi, Marta Vilensky, Jerry 825771 HEADSpAcE – Part B

- Polesel, Ivana Holcatova, Lorenzo Simonato, Cristina Canova, Pagona Lagiou, James D. McKay, Paul Brennan. Genomic analysis of head and neck cancer cases from two high incidence regions. *PLoS One*. 2018 Jan 29;13(1):e0191701.
2. **Perdomo S**, Avogbe PH, Foll M, Abedi-Ardekani B, Facciolla VL, Anantharaman D, Chopard P, Calvez-Kelm FL, Vilensky M, Polesel J, Holcatova I, Simonato L, Canova C, Lagiou P, McKay JD, Brennan P. Circulating tumor DNA detection in head and neck cancer: evaluation of two different detection approaches. *Oncotarget*. 2017 Aug 7;8(42):72621-72632
 3. Torres Á, Oliver J, Frecha C, Montealegre AL, Quezada-Urbán R, Díaz-Velásquez CE, Vaca-Paniagua F, **Perdomo S**. Cancer Genomic Resources and Present Needs in the Latin American Region. *Public Health Genomics*. 2017;20(3):194-201.
 4. **Perdomo S**, Roa GM, Brennan P, Forman D, Sierra MS. Head and neck cancer burden and preventive measures in Central and South America. *Cancer Epidemiol*. 2016 Sep;44 Suppl 1: S43-S52.
 5. **Rodriguez-Urrego PA**, Dogan S, Lin O. Cytologic findings of mammary analogue secretory carcinoma arising in the thyroid. *Diagn. Cytopathol*. 2017 Jun;45(6):552-556.

Relevant projects

1. Mutational profile associated with recurrence of disease and survival in patients undergoing thyroidectomy for papillary thyroid cancer in the Fundación Santa Fé de Bogotá- University El Bosque National Colciencias, 2018-2020, 176,1413 Euros
2. Genomic characterization of potentially malignant lesions of the oral cavity and its association with the presence of human papillomavirus (HPV) – GenOPreV-National-University El Bosque, 2018-2020, 85,077 Euros
3. Evaluation of TLE-1 as a marker in Synovial Sarcomas at the Fundación Santa Fé de Bogotá- National-University Los Andes, 2016-2018, 16,000 Euros
4. Identification of germinal mutations in 143 genes of susceptibility to cancer in patients with hereditary breast and ovary cancer syndrome (HBOCS) in Latin America -LACAM-International-Conacyt, Mexico, 2017-2021, 189,963 Euros

Infrastructure and facilities available for HEADSpAcE

El Bosque University has a research facility with laboratories for all research teams, which have common platforms and equipment for all molecular biology assays proposed in this project: Centrifuges, Laminar flow hoods, Freezers -20C and -80C, an 8 color-Flow cytometer, Incubators, Cell culture rooms. Targeted sequencing in plasma samples will be performed using the existing NGS sequencing platform in our institution and Hardware and software resources for bioinformatics analysis. (A local bioinformatic cluster RedHat operating system, 32 cores, 120GB RAM and 5TB HD) Additional necessary equipment to ensure quality of the DNA extractions, library preparation and quantification is already in place and has been validated by other research groups at the University: Pre-PCR and post-PCR rooms, Bioanalyzer, real time PCR thermocyclers, electrophoresis chambers, transilluminator, thermocyclers, analytical balances and heat blocks.

The pathology department at University Hospital Fundación Santa Fé de Bogotá has high technology equipment for both sample processing, freezing and rapid processing, as well as specialized studies in flow cytometry, molecular biology, immunofluorescence, immunohistochemistry and electron microscopy. Performs more than 32,000 tests per year, including surgical pathology studies, cytology, autopsies, immunofluorescence, electron microscopy, flow cytometry and has a panel of approximately 147 markers for immunohistochemical studies.

Participant 13.

University of the Republic (UdelaR)

Uruguay

Description of participating institute

Research expertise and research environment

The University of the Republic (UdelaR) is the largest Uruguayan university, with about 90.000 students and more than 8000 employees (academic, administrative and technical staff), Research and training in oncology is performed in six hospitals and head and neck oncology patients are centralized in three of them. These hospitals work together and below the same clinical guidelines and database.

Our group has participation in several collaborative studies and consortium like InterCHANGE study.

Overview of research activities

UdelaR has a large experience in cancer research. We count with facilities to perform molecular studies in the Laboratory of Molecular Epidemiology in the Hospital de Clínicas and develop a very strong collaboration with the Institute Pasteur of Montevideo IPMONT.

Ours principal focus of interest is the relation between epidemiology and access to care in head and neck cancer, these aspects have a strong relation with results and quality of care in this population, and the information in LATAM is scare.

Role in the proposal and relevant infrastructure

UdelaR will participate in WP1 and WP2 by contributing to the follow-up of InterCHANGE patients, recruitment of patients newly diagnosed with a head and neck cancer and contributing to the conduct, statistical analysis and interpretation of evidence related to late stage at presentation, the role of socio-economic determinants, implementation of clinical guidelines for treatment of head and neck cancer, and disseminating HEADSpAcE research findings in the broader Uruguay context (WP8).

Role of key scientific people

Dr Mauricio Cuello (male)

Dr Cuello is associate professor in Medical Oncology at UdelaR. His main research interests are in cancer epidemiology, life-course epidemiology, molecular epidemiology and quality of care. He is the coordinator of Head and Neck cancer group.

Dr Cuello is involved in a number of international consortia, including CLICaP (LATAM Lung cancer consortium), InterCHANGE on head and neck cancer and He is principal investigator in epidemiological and clinical studies.

Dr Ricardo DÁlbora (male)

Dr DÁlbora is full professor in Head and cancer unit at Hospital the Clínicas (Regional Centre for Head and Neck cancer treatment). He has coordinated and participated in a large number of population-based studies and consortia on occupational, as InterCHANGE.

Ms Valentina Lestido (female)

Ms Lestido is assistant professor in the Nursing School at UdelaR. Her main research interests include quality and access care, she is specialist in database management and also trained in nursing care in radiotherapy.

Recent, relevant publications

1. Corrales-Rodríguez L, Arrieta O, Mas L, Báez-Saldaña R, Castillo-Fernández O, Blais N, Martín C, Juárez M, Khanna P, Ramos-Esquivel A, Bacon L, Rojas L, Wills B, Oblitas G, Pérez MA, **Cuello M**, Cardona AF; CLICaP. An international epidemiological analysis of young patients with non-small cell lung cancer (AduJov-CLICaP). *Lung Cancer*. 2017 Nov;113:30-36.
2. Cardona AF, Arrieta O, Zapata MI, Rojas L, Wills B, Reguart N, Karachaliou N, Carranza H, Vargas C, Otero J, Ar-chila P, Martín C, Corrales L, **Cuello M**, Ortiz C, Pino LE, Rosell R, Zatarain-Barrón ZL; CLICaP. Acquired Resistance to Erlotinib in EGFR Mutation-Positive Lung Adenocarcinoma among Hispanics (CLICaP). *Target Oncol*. 2017 Aug;12(4):513-523.

3. Cardona AF, Rojas L, Wills B, Arrieta O, Carranza H, Vargas C, Otero J, Corrales-Rodriguez L, Martín C, Reguart N, Archila P, Rodríguez J, **Cuello M**, Ortíz C, Franco S, Rolfo C, Rosell R, on behalf of the CLICaP. BIM deletion poly-morphisms in Hispanic patients with non-small cell lung cancer carriers of EGFR mutations. *Oncotarget*. 2016 Sep 19;7(42):68933-68942.
4. Arrieta O, Cardona AF, Martín C, Más-López L, Corrales-Rodríguez L, Bramuglia G, Castillo-Fernandez O, Meyer-son M, Amieva-Rivera E, Campos-Parra AD, Carranza H, Gómez de la Torre JC, Powazniak Y, Aldaco-Sarvide F, Var-gas C, Trigo M, Magallanes-Maciel M, Otero J, Sánchez-Reyes R, **Cuello M**. Updated Frequency of EGFR and KRAS Mutations in NonSmall-Cell Lung Cancer in Latin America: The Latin-American Consortium for the Investigation of Lung Cancer (CLICaP). *J Thorac Oncol*. 2015 May;10(5):838-43.
5. Goss PE, Lee BL, Badovinac-Crnjevic T, (...) **Cuello M**, Fresco R, Reis RM, Masera G, Gabús R, Ribeiro R, Knust R, Ismael G, Rosenblatt E, Roth B, Villa L, Solares AL, Leon MX, Torres-Vigil I, Covarrubias-Gomez A, Hernández A, Bertolino M, Schwartzmann G, Santillana S, Esteva F, Fein L, Mano M, Gomez H, Hurlbert M, Durstine A, Azenha G. Planning cancer control in Latin America and the Caribbean. *Lancet Oncol*. 2013 Apr;14(5):391-436.Reference

Relevant projects

1. Metformin in stage IV non-small cell lung cancer. Randomized clinical trials to compare metformin plus chemotherapy versus chemotherapy in stage IV lung cancer. PI: Dr. Mauricio Cuello.
2. HPV in lung cancer in Uruguay. PI: Dr. Mauricio Cuello.
3. InterCHANGE. UdelaR collaboration with IARC. Study of HPV in five LATAM countries. Funds: IARC. Uruguayans PI: Mauricio Cuello and Ricardo DÁlbora Project
4. MicroRNA as prognostic in lung cancer. UDELAR-IPMONT. Funds. National Agency of Innovation.

Infrastructure and facilities available for HEADSpAcE

The UdelaR is present in the cluster of public hospitals in Uruguay where the head and neck cancer group develops clinical activities and the group centralized the recruitment of patients. These hospitals have the computational requirements (hardware and software) to store, process and analyses data with high performance, security, stability and control. The Molecular Laboratory is part of a group of laboratories with core facilities. The laboratory is fully equipped to adequately process of biological samples and to perform molecular biological analyses. The UdelaR also developed collaboration with the Institute Pasteur in Montevideo (IPMONT).

UdelaR is present at National Cancer Institute where is available a biobank created in 2016 and store tissue samples.

Participant 14.	Institute of Oncology Angel H. Roffo (IOAR)	Argentina
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Description of participating institute

Research expertise and research environment

The Institute of Oncology “Angel H. Roffo” (IOAR) is one of the four medical centers that belong to the University of Buenos Aires. It is entirely devoted to the treatment of cancer patients since 1922. It assists 6,500 patients per year. It is the first Academic Hospital in Argentina devoted to cancer with a medical department and research facilities. Besides, it is part of the University of Buenos Aires School of medicine and the post graduate carriers in several oncology specialties.

The IOAR “Guidelines for Oncology: Diagnosis, treatment and follow-up of cancer” are updated every two years *Pautas en Oncología. Diagnóstico, tratamiento y seguimiento del cáncer* (<http://institutoroffo.org/nuevaweb/pautas-en-oncologia/>).

The IOAR has, Multidisciplinary Functional Units for specific tumor location. Each one is involved in the attention with integrated, specialized, and coordinated treatment, based on institutional protocols guided by state-of-art scientific knowledge. IOAR has experience in multinational trials lead by well-known consortiums, such as InterCHANGE on head and neck cancer, or INHANCE.

The IOAR Biobank was created in 2012. Since 2003, a hospital-based cancer registry is operating. This belongs to the National Network of Hospital Cancer Records (RITA- National Cancer Institute INC).

Overview of research activities

The research area has been involved in translational research since many years. Its Departments are: Immunobiology, cellular biology, animal care facilities, epidemiology.

The Department of Epidemiology and environmental carcinogenesis is participating in ongoing trials studying incidence, distribution, ethnic aspects, molecular differences in head and neck cancer and breast cancer. Such trials include: InterCHANGE study, Clínic utility of liquid biopsy in the surveillance of HPV negative head and neck tumors, USLACR-NCI United States-Latin America Cancer Research Network. Molecular Profile of Clinical Stage II and III Breast Cancer in Latin American Women Receiving Standard Reference Treatment.

Role in the proposal and relevant infrastructure

IOAR will participate in WP1, WP2, WP4 and WP8. In particular, we will contribute to the recruitment of new patients diagnosed with head and neck cancer. This will also allow us to strengthen our sample contributed to InterCHANGE. IOAR will continue coordinating the teams involved in Buenos Aires (IOAR, Curie Hospital, Hospital Tornu and associated with the Italian Hospital). IOAR will analyze the association between sexual habits and the risk of head and neck cancer of InterCHANGE (WP4). IOAR will also actively participate in dissemination of HEADSpAcE findings throughout Argentina (WP8).

Role of key scientific people

Dr Marta Vilensky (female)

Dr Vilensky is Head of the Department of Epidemiology and environmental carcinogenesis, Research Area at IOAR, University of Buenos Aires. She also teaches epidemiology at Maimonides University and cancer epidemiology in the post graduated carriers in several oncology specialties at IOAR. Dr Vilensky is the Coordinator of IOAR Cancer Registry since 2003, and Principal Investigator in several epidemiology studies, both national and multicentric, Coordinates the participation of several Hospitals of Buenos Aires involved in the InterCHANGE Study (IOAR, Hospital Municipal de Oncología “Marie Curie”, Hospital de Agudos “Tornu” and associated with Hospital Italiano), as PI in Clínic utility of liquid biopsy in the surveillance of HPV negative head and neck tumors Study, as epidemiologist: Molecular Profile of Clinical Stage II and III Breast Cancer in Latin American Women Receiving Standard Reference Treatment, Survival of patients with head and neck cancer. Joint work of the Registry of tumors and the head and neck Unit.

Dr Javier Oliver (male)

Dr Oliver gets his Ph.D. in Genetics and Evolution, University of Granada, Spain (2008), specialized in Human

Genetics and a Bachelor's degree in Biology at University of Granada, Spain (2003). Since 2015 he leads the molecular cancer epidemiology group at ICBME-IUHIBA (*Instituto de Ciencias Básicas y Medicina experimental - Instituto Universitario del Hospital Italiano*) and he is in charge of the Sequencing lab at HIBA (Hospital Italiano de Buenos Aires). He is an active participant in the Head and Neck International cancer case control study InterCHANGE. Previous research activities: Postdoctoral position at Genetic Cancer Susceptibility Group. IARC-WHO. Lyon 01/2013 to 07/2013. Postdoctoral Position at Institute of Functional Genomics of Lyon. Ecole Normale Supérieure Lyon UMR 5242CNRS/INRA/UCBL/ENS. Lyon, France.

Dr Raul Eduardo Giglio (male)

Dr Giglio graduated in medicine in 1983 at the University of Buenos Aires, School of Medicine. He is specialized in internal medicine and medical oncology. He entered the IOAR in 1989. He is known head of medical oncology in the head and neck cancer unit. He is conducting several randomized trials in this area especially in the combination of immunotherapy and chemotherapy and radiation therapy.

Dr Roque Adan (male)

Dr Roque Adan graduated in medicine in 1979 at the University of Buenos Aires. Specialized in Surgical Oncology and Head and Neck Surgical Oncology. Head of Department of Head and Neck Oncology Surgery and Member in the Head and Neck Cancer Unit Institute of Oncology "Angel H. Roffo" School of Medicine, University of Buenos Aires. Chief of Service Head and Neck Surgery British Hospital of Buenos Aires. Dr Adan is involved in InterCHANGE on head and neck cancer.

Recent, relevant publications

1. Perdomo S, et al. Genomic analysis of head and neck cancer cases from two high incidence regions. *PLoS One*. 2018 Jan 29;13(1):e0191701.
2. Perdomo S et al. Circulating tumor DNA detection in head and neck cancer: evaluation of two different detection approaches. *Oncotarget*. 2017 Aug 7;8(42):72621-72632
3. Lesseur C et al. Genome-wide association analyses identify new susceptibility loci for oral cavity and pharyngeal cancer. *Nat Genet*. 2016 Dec;48(12):1544-1550
4. Fernandez-Cuesta L et al. Identification of Circulating Tumor DNA for the Early Detection of Small-cell Lung Cancer. *EBioMedicine*. 2016 Aug;10:117-23.
5. Boffetta P et al. Mouthwash use and cancer of the head and neck: a pooled analysis from the International Head and Neck Cancer Epidemiology Consortium. *Eur J Cancer Prev*. 2016 Jul;25(4):344-8

Relevant projects

1. IARC-WHO-Lyon. Multicenter Study on Genetic and Molecular Epidemiology of Head and Neck Cancers in Latin America (INTERCHANGE/IARC and GENCAPO/SP). PI: Dr. Brennan, IARC.
2. USLACR-NCI United States-Latin America Cancer Research Network. Molecular Profile of Clinical Stage II and III Breast Cancer in Latin American Women Receiving Standard Reference Treatment ("Perfil Molecular de Cáncer de Mama en Estadío Clínico II Y III en Mujeres Latinoamericanas que reciben Tratamiento Estándar de Referencia
3. INC, Argentinian National Cancer Institute. Financial Assistance to Cancer Research Projects of National Origin. Interdisciplinary study on the diagnostic, therapeutic and end-of-life trajectories of people with cancer ("Asistencia Financiera a Proyectos de Investigación en Cáncer de Origen Nacional". Morbimortalidad por cáncer en Argentina. Estudio interdisciplinario sobre las trayectorias diagnósticas, terapéuticas y el final de la vida de personas con enfermedades oncológicas"). 2012-2013
4. INC, Argentinian National Cancer Institute. Financial Assistance to Molecular Profile of Clinical Stage II and III Breast Cancer in Latin American Women Receiving Standard Reference Treatment ("Perfil Molecular de Cáncer de Mama en Estadío Clínico II Y III en Mujeres Latinoamericanas que reciben Tratamiento Estándar de Referencia") 2014.
5. SECYT Secretaría para la Tecnología, la Ciencia y la Innovación Productiva CONICET Ocurrencia y factores de riesgo para el cáncer en la Argentina. PID 02031.

Infrastructure and facilities available for HEADSpAcE

The IOAR unit of head and neck cancer is integrated by surgeons, radiation oncologist and medical oncologist trained in carrying on research studies which imply recollecting tissue and blood samples as well as epidemiologic data. They are also trained in shipping samples according to international guidelines.

The epidemiology team works jointly and in coordination with the head and neck functional unit. We have interviewers and data entry trained.

The IOAR biobank collections of human biospecimen from the Institution (IOAR). The biobank has a specific objective in promoting scientific collaboration and has developed a clearly defined access pipeline for investigators outside IOAR. The storage facilities include liquid nitrogen (LN2) tanks and freezers (-150°C, -80°C, -20°C).

The research area has its own freezers for the studies in which it is involved.

Participant 15.**University of Tennessee Health Science Center
(UTHSC)****United
States****Description of participating institute****Research expertise and research environment**

The University of Tennessee Health Science Center (UTHSC) in partnership with St. Jude Children's Research Hospital has a wide variety of resources that make this an exceptional environment for Dr Hayes and co-investigators to conduct the proposed work. UTHSC hosts 29 Departments in the College of Medicine in Memphis alone with other sites in Knoxville and Chattanooga. There are six colleges (Dentistry, Graduate Health Sciences, Health Professions, Medicine, Nursing, and Pharmacy) that educate over 800 residents and fellows. There are four teaching hospital partners. UTHSC is undergoing a \$300 million campus renovation and period of growth. The UTHSC Biomedical Sciences Graduate Programs offer Doctor of Philosophy and Masters degrees, granted through the UTHSC College of Graduate Health Sciences, in four separate areas; Integrated Biomedical Sciences, Epidemiology, Biomedical Engineering, and Pharmacology. UTHSC in collaboration with St. Jude Children's Research Hospital has invested tens of millions in cancer and genomics research. St. Jude, in partnership with UTHSC and in collaboration with West Cancer Clinic and Methodist Le Bonheur Healthcare joined forces to recruit co-PI D. Neil Hayes as Scientific Director of the UT-West Institute for Cancer Research and Assistant Dean for Cancer Research. This recruitment represented the single largest investment in cancer in the history of UTHSC.

Overview of research activities

Progress in two key areas of science has provided the foundation for the work in Dr Hayes' group. First, the advent of personal computers along with associated progress in the field of statistical computing greatly accelerated the development of data-rich models of human disease behavior. Second, collaborative efforts across biomedical science have made available the building blocks of normal (i.e. The Human Genome Project) and aberrant genomes (i.e. The Cancer Genome Atlas). To leverage the power of computers to assess alterations in the genome associated with cancer, a host of molecular technologies have become commercially available in recent years. The primary targets of these assays have been nucleic acids (DNA and RNA), although a limited number of protein assays are also included. The technologies allow labs such as ours to make broad and inclusive measurements in samples of alterations in gene expression (RNA), gene dosage (DNA amplification and deletions), gene structure (normal population variants, mutations, alternate splices, fusion genes, and epigenetic modifications), protein abundance and other events such as presence of a pathogen. Primary technologies used in the lab include array-based approaches (gene expression arrays, methylation profiling, SNP chips, CGH, miRNA arrays), sequencing (targeted and deep sequencing / "NextGen"), and immunohistochemistry (including tissue microarrays).

Role in the proposal and relevant infrastructure

UTHSC will lead WP5. With an expanding network of European, North American, and South American scientists, scientists in Dr Hayes' lab at UTHSC will assess socio-economic, logistic, and biologic predictors of diagnosis at late stage based on data from large biorepositories. Ongoing trials such as ARCADE, InterCHANGE, and HN5000 will provide samples from 1000 HNC cases from Latin America and Europe. Genomic sequencing and transcriptomic analysis of these samples will allow for comprehensive analysis of genomic, infectious, and lifestyle risk factors for HNC progression. Data will also be incorporated into VOYAGER work being done through another National Institutes of Health grant through the International Agency for Research on Cancer at the World Health Organization (5-R01-DE025712).

Role of key scientific people**Dr D. Neil Hayes (male)**

Dr Hayes is a leader of WP5. Dr Hayes is a medical oncologist and a prolific genomics researcher for more than a decade. He is currently the Van Vleet Endowed Professor, Division of Medical Oncology and Department of Preventive Health, at the University of Tennessee Health Sciences Center, West Cancer Center that is located in Nashville TN. He is the Scientific Director of UT/West Institute for Cancer Research. Previous to his move to UTHSC in August of 2017, he was a Professor of Medicine and practicing oncologist at UNC-CH for 13 years, where he worked closely with Dr Perou on multiple genomic and oncology based projects. He has numerous current and past grants in cancer genomics including as co-PI (with Dr Perou) for The Cancer Genome Atlas Project. He has

extensive expertise in bioinformatics and its application to the analysis of large databases of gene expression data, coming from both DNaseq and RNAseq, and in the integration of multiple data sets.

Recent, relevant publications

1. Cancer Genome Atlas Research Network. Comprehensive Genomic Characterization of Head and Neck Squamous Cell Carcinomas. *Nature*. 2015 Jan 29;517(7536):576-82
2. Parfenov M, Peadarallu CS, (...) **Hayes DN**, Grandis JR, El-Naggar AK, Meyerson M, Park PJ, Chin L, Seidman JG, Hammerman PS, Kucherlapati R; Cancer Genome Atlas Network. Characterization of HPV and Host Genome Interactions in Primary Head and Neck Cancers. *Proc Natl Acad Sci U S A*. 2014 Oct 28;111(43):15544-9
3. Walter V, Yin X, (...) Shores CG, **Hayes DN**. Molecular Subtypes in Head and Neck Cancer Exhibit Distinct Patterns of Chromosomal Gain and Loss of Canonical Cancer Genes. *PLoS One*. 2013; 8(2): e56823
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Relevant projects

1. The Role of Germline and Somatic DNA Mutations in Oral and Oropharyngeal Cancers, 1R01DE025712-01A1, USA NIH funded through IARC, Brennan PI, Hayes subsite PI
2. Development of a Four-Class, Molecular Subtyping Diagnostic for HPV-negative Head and Neck Cancer., 1R01CA211939-01A1, USA NIH funded Hayes PI, Zevallos, co-PI
3. Network Group Integrated Translational Science Centers Application, U10-CA181009, USA NIH funded Hayes, co-PI, Perou, co-PI
4. Gene Expression Patterns in Human Tumors Identified Using Transcript Sequencing, 3U24CA143848, USA NIH funded Hayes, co-PI, Perou, co-PI
5. VTX-2237 in Patients with Recurrent or Metastatic SCCHN, VRXP-A202 USA Pharmaceutical Association, Hayes PI

Infrastructure and facilities available for HEADSpAcE

Dr Hayes' Laboratory is located in the state-of-the-art University of Tennessee Cancer Research Building and affiliated facilities of UTHSC. As the director of the UT/West Cancer Research Institute and Associate Dean of Cancer for UTHSC, Dr Hayes has direct supervision over 20,000 sq. ft. of wet lab and computational office space consisting of the entire 4th floor of the Cancer Research Building. The lab is currently undergoing complete renovation scheduled to complete in the Fall of 2018 with 12 faculty offices, server room, 5 locked instrumentation and freezer rooms, and approximately 1000 sq. ft. of conference space. Approximately 10,000 sq. ft. is devoted to open floor plan wet lab space with 12 tissue culture (TC) rooms with laminar flow hoods, incubators and chemical hoods. The laboratory is fully-equipped for biochemistry, molecular biology, cellular biology and for genomic analyses as described in the equipment section. Dr Hayes has temporary lab space in the newly opened Translational Science Research Building (TSRB) joined to the Cancer Research Building by bridges on every floor.

Dr Hayes has additional laboratory space at the St. Jude Children's Research Hospital, consisting of an office (200 sq. ft.) and dry lab space 200 sq. ft. for students, post-doctoral fellows, and staff. There is total seating space for 4 researchers within the offices of the Department of Computational Biology on the sixth floor of the newly opened Kay Research and Care Center. Dr Hayes has access to the core facilities of the Computational Biology Genomics Laboratory which occupies 1,530 sq. ft., consisting of 4 rooms and one office. These spaces include a primary lab containing 10X Genomics single-cell equipment, library prep room, a post PCR/ library amplification room, an automation room containing liquid handlers, and a sequencing equipment room including one NovaSeq 6000, one HiSeq 4000. As a member of St. Jude, he has access to all cores.

UTHSC Computers: We have approximately 8 other systems that are devoted mainly to web service applications, including (prospectively) the Omics Portal for Addictome Research (OPAR) web service for NIDA, current GeneNetwork servers (production, development, and staging); two servers being used to test GPU hardware, a Galaxy mirror, and two UCSC Genome Browser mirrors. All clusters and servers are housed in UTHSC's main machine room of the Lamar Alexander Building. We also maintain file servers (on the clusters) to archive array,

FASTQ, BAM and SAM alignment files of the type that will be used for TIM and OPAR. We have recently added two high performance GPU systems (Tesla K20 and K80 systems from Penguin Computing). The Penguin Relion 2800GT server (2013) has 2 E5-2600 CPUs and a NVIDIA Tesla K20X GPU and incorporates 2688 CUDA cores. The new system (2015) has 24 GB of shared RAM (needed for large matrix operations) and 4992 CUDA cores. GN2, OPAR, and all servers are housed in the main UTHSC machine room in the Lamar Alexander Building. This is a physically secure location with raised floors and an advanced fire extinguishing system. We have access to this space for upgrades and periodic hardware maintenance. This computing facility contains three of our 48U racks. Each rack has a mix of Dell PowerEdge servers (from low end R610s to higher performance R620 and R815 systems) and dedicated Cisco switches. We have multiple production, staging, and development versions of GN (see GeneNetwork on GitHub). Mirrors in Europe (HZI, Germany) and EC2 are synchronized by our systems administrator, Dr Lei Yan. GN is a fully open system (AGPLv3). A full copy of the GN production server and database is maintained on Amazon EC2 (North Carolina). A collaborator of Dr Hayes, Dr Williams, manages four Linux clusters (96 to 192 core systems) and several other servers.

Oak Ridge National Lab: The University maintains a secure, HIPAA-compliant network for all on-campus computers. We also have ownership of a large HIPAA data enclave at the Advanced Computing Facility (ACF) at Oak Ridge National Labs that is currently budgeted for 5 PB and ultimately planned for 20 PB, all with ultra-fast network access. Integrated with these storage systems are the compute clusters: Newton and Beacon (Cray Xtreme-X) systems. These expanded and reconfigured compute resources comprise approximately 5500 cores (mainly Xeon E5-2670s and 2680s) operating within full HIPAA and ISO 27001 compliance in our secure data enclave.

St. Jude High Performance Computing Facility (HPCF): Through St. Jude, investigators have access to the High Performance Computing Facility (HPCF) research cluster consisting of 295 Xenon processors and 6400 cores attached to DataDirect Networks (DDN) GridScaler implementation of the IBM Spectrum Scale (GPFS) parallel file system. This environment provides each compute node with high bandwidth, low latency access to a dedicated 6.7 PB of storage. All compute run the Red Hat Enterprise Linux 6 operating system, and are connected to an FDR InfiniBand fabric for message passing and high-speed storage access. The Platform LSF 10 job workload manager provides job dispatch and management, and Bright Cluster Manager provides provisioning and monitoring functions. The files system is configured with replicated metadata in dedicated flash-based storage controllers. This storage resource is also available over NFS and SMB protocols through multiple 40 Gigabit Ethernet links, allowing access from researcher workstations, labs, and application servers.

For scale-out network attached storage (NAS) use, a second DDN GridScaler environment is available, providing 3.8 PB of usable capacity for research data. This resource includes multiple NFS and SMB protocol nodes providing multiple 40 Gigabit Ethernet links, and provides lab environments, application servers, and research workstations with storage for a variety of workloads. The HPCF research cluster can also access this storage resource for lightweight file access. Data protection for all storage systems is provided via local disk pools and multiple encrypted tape copies, which are generated daily and sent to 2 separate off-site vault facilities. In addition, an 8 PB (usable) object store for data archive is integrated with this environment.

All compute nodes have access to a 56 Gigabit per second FDR InfiniBand fabric, at a maximum 2:1 blocking ratio. The parallel file system environment has non-blocking access to the InfiniBand interconnect and uses it as a primary data path, allowing increased bandwidth and reduced overhead for access to large datasets. The HPCF research cluster includes a redundant 10 Gigabit Ethernet core for standard networking access and management, with Gigabit Ethernet to each compute node for NFS and management connectivity. The large-scale research storage environment is integrated with a 40 Gigabit Ethernet dedicated network for integration with distributed data acquisition and analysis across the St. Jude campus.

The HPCF maintains systems with streamlined connectivity to St. Jude's external Internet connections (primary 1 Gbps, standby 1 Gbps), as well as Internet2 research networking (10 Gbps). An IBM Aspera file transfer service with high availability is available to support collaborations requiring large-scale data transfers.

The HPCF provides application, database, and ancillary analysis systems to researchers using a highly redundant VMware virtualization infrastructure. Information Services has dedicated teams for storage, backup, networking, data center facilities, virtualization, and information security. These institutional resources provide a reliable platform for delivery of software and services that used in support of the cluster infrastructure detailed above.

4.2 Third parties involved in the project (including use of third party resources)

a) Participant 2 - ICO

Does the participant plan to subcontract certain tasks (please note that core tasks of the project should not be sub-contracted)	No
If yes, please describe and justify the tasks to be subcontracted	
Does the participant envisage that part of its work is performed by linked third parties ²	No
Does the participant envisage the use of contributions in kind provided by third parties (Articles 11 and 12 of the General Model Grant Agreement)	Yes
If yes, please describe the third party and their contributions	
<p>The Fundació Institut d'Investigació Biomèdica de Bellvitge (IDIBELL) is a third party of ICO assisting in administrative and financial tasks as foreseen by the Specific case for Foundations in Article 11 of the Annotated Model Grant Agreement (3 July 2018 version) without cost, including issues related to employment and payment of hired personnel, purchase of consumables, etc. This case has been recently moved from Article 12 to Article 11. This relationship is governed by a prior agreement between both institutions signed on 02/10/2007.</p> <p>IDIBELL is a non-profit research institution which carries out and manages research activities in the area of biomedicine – both basic and clinical research. It manages research activities of researchers at the Catalan Institute of Oncology (ICO) at l'Hospitalet site. This implies that during the project:</p> <ul style="list-style-type: none"> - The coordinator will directly transfer to IDIBELL the pre-financing, interim and final payments - The whole budget (EC contribution) for ICO will be financially handled by IDIBELL - IDIBELL is going to be in charge of the whole management of the project, which means that personnel from various departments are going to be involved during the whole life cycle of the project. For instance, the Post Award Office is going to manage the financial and administrative aspects of the project, including the preparation of the Financial Reports; the Purchasing Department is going to manage all purchases charged to the project; the Accounting Department is going to manage the payment of the invoices; the Human Resources Department is going to manage the new labour contracts; the Pre-Award and Legal Departments are going to revise the Consortium Agreement. <p>This way of participation has previously been approved for the following active H2020 collaborative projects: ANTI-SUPERBUGS (GA no. 688878); EDIREx (731105); EUREST-PLUS (681109); MoTriColor (635342) and TackSHS (681040).</p> <p>This will involve work packages 1, 2, 3, and 4. As an in-kind contributor, ICO will not claim any costs for IDIBELL and the estimated budget is then 0€</p>	
Does the participant envisage that part of the work is performed by International Partners ³ (Article 14a of the General Model Grant Agreement)?	No
If yes, please describe the International Partner(s) and their contributions	

b) Participant 6 - UGLA

Does the participant plan to subcontract certain tasks (please note that core tasks of the project should not be sub-contracted)	No
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² A third party that is an affiliated entity or has a legal link to a participant implying a collaboration not limited to the action. (Article 14 of the [Model Grant Agreement](#)).

³ 'International Partner' is any legal entity established in a non-associated third country which is not eligible for funding under Article 10 of the Rules for Participation Regulation No 1290/2013.⁴ A third party that is an affiliated entity or has a legal link to a participant implying a collaboration not limited to the action. (Article 14 of the [Model Grant Agreement](#)).

If yes, please describe and justify the tasks to be subcontracted	
Does the participant envisage that part of its work is performed by linked third parties ⁴	Yes
<p>UGLA has a Linked Third Party arrangement with the Greater Glasgow and Clyde Health Board (GGHB) and this has been accepted by DG research for previous Horizon 2020 Projects. <i>Background papers attached.</i></p> <p>Using this Linked Third Party arrangement, UGLA will access the Greater Glasgow and Clyde Health Board Clinical Research Facility pool of Research Nurses to deliver part of the objectives of Work package 2 (Task 2.1 Phase 1) set out in Work Package 2. This work is the recruitment of Glasgow centre cohort of patients with head and neck cancer and data collection (clinical data, questionnaires, and blood samples).</p> <p>UGLA has agreed a budget of €62,500 (€50,000 Direct Costs + €12,500 Indirect Costs) with the Greater Glasgow and Clyde Health Board, for provision of personnel to undertake the duties specified above.</p>	
Does the participant envisage the use of contributions in kind provided by third parties (Articles 11 and 12 of the General Model Grant Agreement)	No
If yes, please describe the third party and their contributions	
Does the participant envisage that part of the work is performed by International Partners ⁵ (Article 14a of the General Model Grant Agreement)?	No
If yes, please describe the International Partner(s) and their contributions	

4.3 Financial support to third parties

N/A.

⁴ A third party that is an affiliated entity or has a legal link to a participant implying a collaboration not limited to the action. (Article 14 of the [Model Grant Agreement](#)).

⁵ ‘International Partner’ is any legal entity established in a non-associated third country which is not eligible for funding under Article 10 of the Rules for Participation Regulation No 1290/2013.