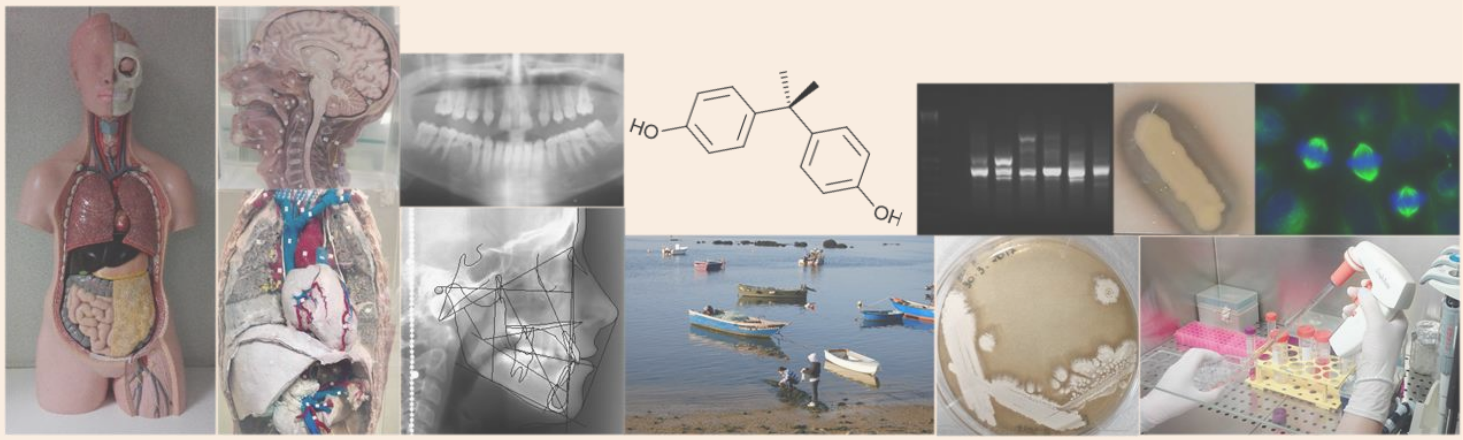
VII WORKSHOP IINFACTS



ABSTRACTS BOOK

20 JULY 2017 | GANDRA

Welcome

Welcome to the VII Workshop IINFACTS.

Created with the main objective of spreading among the CESPU scientific community the most recent research carried out in its research unit, this event also intends to promote the peer discussion about the main topics focused on the four areas of interest of the IINFACTS, as well as to potentiate future collaborations between the elements involved in those areas of interest.

We wish you a beneficial event.

The organising committee,

Ana Cristina Henriques, António Ferraz, Bruno Sarmento, Daniela Paiva, Gonçalo Castilho, Hassan Bousbaa, Joana Tavares, Maria João Calheiros Lobo, Miguel Gomes, Rui Azevedo, Teresa Costa, Vanessa Marcelino, Virgínia Gonçalves, Viviana Vasconcelos

SCIENTIFIC PROGRAM

VII WORKSHOP IINFACTS | 20 JULY 2017

ANFITEATRO III

09.00h	**OPENING SESSION** Prof. Doutor António Almeida Dias, Presidente da Direção da CESPU Prof. Doutor Jorge Brandão Proença, Magnífico Reitor do IUCS Profª. Doutora Raquel Esteves, Diretora da Escola Superior de Saúde do Vale do Sousa Prof. Doutor Vítor Seabra, Coordenador do Gabinete de Investigação e Desenvolvimento (GID) Prof. Doutor Hassan Bousbaa, Diretor do IINFACTS
SESSION I CLINICAL RESEARCH Oral Diseases Moderator: Corsina Velazco Henriques & José Júlio Pacheco	
09.30h	**Teresa Pinho**: Stability of orthodontic treatment in malocclusions in general and dental agenesis in particular.
09.40h	**Marta Relvas:** Microbiological validation of an oral health scale of infectious-inflammatory potential through 16S rDNA metagenomic techniques.
09.50h	**José Manuel Mendes**: Design and construction of a new "attachment" used in oral rehabilitation over implants.
10.00h	**Cristina Coelho**: In vivo evaluation of the antimicrobial effect of the Nd: YAG laser versus sodium hypochlorite in endodontic pathogens.
10.10h	***Coffee Break***
SESSION II CLINICAL RESEARCH Cardiovascular Diseases | Psychology and Health | Healthcare Moderator: Isabel Araújo & José Carlos Rocha	
10.30h	**João Paulo Venâncio**: Acute effects of exercise on circulating levels of endothelial progenitor cells in patients with coronary artery disease.
10.40h	**Sandra Leal**: Inflammatory biomarkers and neurocognition in cardiovascular diseases.
10.50h	**Maribel Teixeira**: Characterization of posologic instruction patterns in dermatology.
11.00h	**Maria Manuela da Silva Leite**: Caregivers of the terminally ill: How to reduce the impact of the loss?

SESSION III ENVIRONMENTAL RESEARCH Applied Chemistry | Applied Microbiology Moderator: Paolo De Marco	
11.10h	**Maria Elizabeth Tiritan**: Enantioselective synthesis of chiral xanthone derivatives and anti-inflammatory evaluation.
11.20h	**Alexandra Viana da Costa**: Evaluation of antiparasitic activity of Nitazoxanide incorporated in polymeric and lipidic nanosystems.
11.30h	**Cláudia Ribeiro**: Monitorization of mycotoxins and heavy metals in sediments of the estuaries of the Rivers Douro and Ave.
11.40h	**Sónia Marisa Machado**: New anti-Protozoa agents and Aspartic peptidases as a chemotherapeutic target.
11.50h	**Sandra Quinteira**: Exploiting the potential of fish mucus.
SESSION IV Forensic Science Research In vivo | Postmortem Moderator: Ana Teixeira	
12.00h	**Ricardo Dinis**: Acute administration of tramadol and tapentadol induces dose-dependent toxicity in Wistar rats.
12.10h	**Susana Coimbra**: Pruritus mediators in cutaneous T-cell lymphomas, mastocytosis and psoriasis.
12.20h	**Almoço**
SESSION V DRUG DELIVERY, DISCOVERY & TOXICOLOGY Cancer Research |Drug Delivery Moderator: Maribel Teixeira	
14.30h	**Hassan Bousbaa**: The Mitotic Protein Spindly as a Cancer Therapeutic Target.
14.40h	**Luís Monteiro**: Biomarkers on potential malignant disorders and oral squamous cell carcinomas.
14.50h	**Odília Queirós**: Unravelling the molecular mechanisms underlying metabolic modulators inhibition of tumor progression and treatment resistance.
15.00h	**Bruno Sarmento**: Bioengineered FcRn-targeting nanoparticles for intestinal delivery of biopharmaceuticals.
15.10h	**José Carlos Andrade**: Development of lipid-based particles for the encapsulation of dietary bioactives.
15.20h	**Sandra Leal**: Hepatic Effects of Long-term Tamoxifen Administration to Cycling Female Rats.
15.30h	***Coffee Break***
15.45h	**SESSÃO DE ENCERRAMENTO** | Vítor Seabra – Coordenador do GID
16.00h	Análise Crítica do Funcionamento Geral do IINFACTS e das suas linhas de investigação

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Stability of orthodontic treatment in malocclusions in general and dental agenesis in particular

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Maxillary lateral incisors agenesis (MLIA), a frequent tooth agenesis, creates esthetic problems with psychologic, orthodontic and prosthetic factors which are a lifetime problem, involves long term maintenance and family counselling. Previous studies revealed MLIA prevalence at 1.3% in a Portuguese population.
Several genes have been identified as being expressed during odontogenesis in some signaling pathways. Several association studies comprising different traits have found significant results with the identification of dental agenesis susceptibility genes and unravelling the mechanisms and pathways in which it would be possible to develop therapeutic strategies.
Treatment plans to deal with MLIA patients are complex and require an interdisciplinary approach and long-term predictability. Early diagnosis and effective clinical management of MLIA are important because many invasive procedures may then be avoided.
Orthodontic space closure may involve operative dentistry turning a canine into a lateral incisor or a first premolar into a canine, thereby improving the anterior tooth harmony. Such approach can be done at an early age, with necessary long-term adaptations occurring in synchrony with the patients own teeth.
If space opening is indicated, two restorative approaches can be done: single tooth implant or resin-bonded bridges (RBBs). Dental implants are commonly used once skeletal maturity is reached, but adequate alveolar ridge dimensions is a prerequisite. RBB constitutes a minimal invasive approach for replacing MLIA and can serve either as a definitive or interim prosthesis until implant rehabilitation is permitted.
Our future goal will be to develop a continuous research from origin and diagnostic to treatment of MLIA patient, with a multidisciplinary team of geneticists, engineers, chemists, dentists and a dental technician. It will be expected to obtain not only satisfactory esthetical and functional results with minimal invasive approach (to close or open space), but also consider them as a non-provisional approach.

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Microbiological validation of an oral health scale of infectious-inflammatory potential through 16S rDNA metagenomic techniques

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Little has been published in the dental literature on the combination of distinct variables in the design of oral health scales. Particular interest in the idea of representing the oral health status in a single numerical value arose with the development of "Periodontal Medicine", which aims to establish correlations between infectious/inflammatory disorders of the oral cavity and the appearance of certain systemic diseases. In this thesis, we propose a new global oral health scale that establishes a single value for the infectious potential of the oral cavity, which has its clinical expression in the form of local and focal infections. The scale incorporates dental and periodontal variables organised according to objective and tested indices that reflect to a certain degree the presence of the principal infectious disorders of the oral cavity, caries and periodontal disease. The different grades of the scale have been correlated with the presence and concentration of various bacterial species of the salivary flora.

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Design and construction of a new "attachment" used in oral rehabilitation over implants

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Partial or total edentulism impairs masticatory function significantly, constituting an important oral health problem in a large part of the adult population. For more than 100 years, conventional dental prostheses were the only treatment available for edentulism.
Traditional treatments comprising prosthetics are often insufficient to restore complete masticatory function and may adversely affect nutrition, physical appearance, and self-esteem.
These problems generally worsen with age because, to the loss of teeth, the reabsorption of the alveolar bone makes it difficult to rehabilitate through conventional removable prostheses. In order to overcome these limitations and facilitate masticatory function, the use of attachments between the prosthesis and endosseous dental implants has become a common clinical practice.
Mandibular overdentures retained by 2 implants are recognized as the first treatment option for edentulous patients, as stated in their consensus statement by McGill University (Canada), published in 2002 and the British Society for the Study of Prosthetic Dentistry, in their York Consensus Statement, published in 2009. When compared to conventional full dentures, they provide greater patient satisfaction, greater masticatory capacity, and preservation of residual crest height. On the other hand, overdentures on 2 implants are more cost-effective than conventional dentures and other types of prostheses retained by implants.
Overdentures are subject to complex three-dimensional movements as a result of masticatory loading, and the presence of saliva and other substances in the oral environment may alter the physico-chemical and hence biomechanical properties of the attachments.
There are a large number of available attachments provided by a large number of manufacturers around the world. This can be quite confusing for the inexperienced clinician. This problem is even greater because their choice and indication are based primarily on opinions and clinical experience and not on actual evidence and scientific findings.
The main objective of this project is to design and build a new attachment used in oral implant rehabilitation.

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In vivo evaluation of the antimicrobial effect of the Nd: YAG laser *versus* sodium hypochlorite in endodontic pathogens

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Root canal therapy (RCT) is the dental procedure related to the preservation of natural teeth when pulp and its surrounding tissues, are affected. One of the most important steps of RCT comprises cleaning, disinfecting and shaping the root canals (RC) to fill them with an inert substance. The success of this therapy is dependent on complete elimination of microorganisms from RC. To achieve this, cleaning and debridement of the canals, with a range of irrigating and disinfecting solutions have been used, amongst which predominates sodium hypochlorite (NaClO) in concentrations ranging from 0.2-5%. Also, the Nd:YAG laser has been used to remove smear layer and to disinfect RC, based on the thermal heating of the bacterial environment and local heating inside bacteria . The advantage of the Nd:YAG in RC disinfection is its significant bactericidal effect up to 1 mm into the dentine. Studies on comparison of antibacterial effects of Nd:YAG with NaClO showed effectiveness of both, with a better effect for NaClO. However, the main studies are realized *in vitro* and ex vivo, with inoculation of specific microorganisms in RC of extracted teeth. In this work, we evaluated *in vivo* the effect of antimicrobial reduction in RCT with microbiological culture from three experimental groups (G) of patients. G1- NaClO; G2 - Nd:YAG laser; G3- NaClO + Nd:YAG laser. We have done microbiological control before and after the procedures of disinfection and/or irradiation. Our results showed a reduction of the total aerobic and anaerobic microorganisms of 90.86%, 88.60% and 99.92%, respectively in G1, G2 and G3, suggesting therefore advantages on adjunct therapy, ND: YAG laser + NaClO for RC disinfection.

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Acute effects of exercise on circulating levels of endothelial progenitor cells in patients with coronary artery disease

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Inflammatory biomarkers and neurocognition in cardiovascular diseases

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Cardiovascular diseases (CVD) remain the main cause of mortality and disability in worldwide. CVD increases the risk of ischemic stroke, vascular dementia and Alzheimer's disease. Even before dementia, CVD are associated with a subtle effect on brain structure and functioning, and on cognitive performance. Moreover, clinical depression and depressive symptoms worsen the prognosis of CVD. Inflammation and L-tryptophan metabolites are two strong candidates for the link between CVD and cognitive decline. Indeed, inflammatory mediators can promote the tryptophan metabolism to shift towards kynurenine pathway and its metabolites have been closely linked to several neurological diseases. Yet, studies linking kynurenine pathway activation, cognitive dysfunction and heart failure are sparse. In this study, we will investigate the lifestyle risk factors and cognitive function of patients with heart failure and evaluate if tryptophan metabolites in serum and urine are altered, or if altered ratios of metabolites indices predict cognitive decline. This study was approved by the Ethical Committee of Hospital Padre Américo/CHTS, EPE. Psychological and nutritional assessment and, blood and urine collection will be obtained in all patients with systolic heart failure indicated by the cardiologist. Psychological assessment will embrace a sociodemographic and clinical questionnaire, neurocognitive functioning, emotional functioning. Nutritional assessment will include anthropometric evaluation and lifestyle questionnaire, (eating frequency, alcohol consumption, smoking habits and physical activity). Serum and urine samples will be assayed for tryptophan and its metabolites by HPLC. The kynurenine pathway may reveal new aspects of the complex interaction between tryptophan metabolism and cognitive functions and leading to potential new targets for the treatment of cognitive decline in CVD patients.

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Characterisation of posologic instrution patterns in dermatology

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Dermatosis are among the most common diseases worldwide. Approximately one third of the population is affected by a skin condition through its life. Posologic recommendations associated with the prescription in Dermatology are insufficiently characterized, with no data available on the situation in Portugal. Failure of the indication of the duration of treatment, the application site and the dose were reported as some of the gaps of dermatological prescriptions[1]. Unclear and incomplete posologic instructions specific to the dermal administration may contribute to the clinical ineffectiveness of topical medicines. The aim of this study was the characterization of the posologic instruction patterns in dermatology, aiming to establish guidelines for proper use of the topical medicines and promotion of treatment adherence. The perception of patients regarding posology of dermatological treatments and corresponding behavioural patterns was evaluated as well as their perception of the use of measuring dose devices on the administration of topical medicines.

Results indicate some discrepancies between instructions provided by physicians and perceived by patients, in particular regarding to dose instructions, revealing the need to optimize posologic instrution patterns in dermatology. In addition, in the community pharmacy the reinforcement of the dose instructions may also contribute to the correct use of the medicines and the promotion of the adherence to topical treatment in chronic dermatosis.

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Caregivers of Terminally ill: How to reduce the impact of loss?

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Death is the last stage of the life cycle. Although normative, it is often surrounded by feelings of anguish, loss, among others, arising from the difficulties of accepting existential finitude. In terminal cancers, this process begins well before the death of the patient, covering the patient and his relatives. There are many factors that influence the process of adaptation to the disease by them, as well as the process of grief. Consequently, the impact of the disease does not end with the death of the patient, imposing on the caregiver the need to adapt to the loss, with risk of psychological morbidity. Therefore, the main objective of the present investigation is to identify predictors of difficulties in adapting surviving family caregivers, and subsequently the development of a program of psychological intervention that promotes the process healthy grief. In this context, the research is composed of three phases: Phase 1: period of palliative / terminal illness; Phase 2: Grief process; And Phase 3 - Grief recovery process. In the first phase, participates the patient and his / her relative, being a group of patients (clinical group) the target of a psychological intervention based on the Chorchinov Dignity Model. Family caregivers are evaluated with a set of psychological instruments. The second phase begins one month after the death of the patient and is intended throughout the same to evaluate the process of mourning. The third and last phase begins nine months after the death of the patient, at a time when it is expected to resolve the grieving process.

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Enantioselective synthesis of chiral xanthone derivatives and anti-inflammatory evaluation

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Cyclooxygenases (COX-1 and COX-2) are two important isoforms, in which, COX-2 is expressed in various pathophysiological processes, like inflammation and cancer. COX-2 has been identified as novel cancer chemo-preventive and therapeutic target being the searching of new COX-2 inhibitors of great interest. Natural or synthetic origin xanthones can present a variety of physiological/pharmacological activities, depending on the nature of the substituent in the dibenzo-γ-pyrone scaffold. Nowadays, xanthones are of recognized relevance to human therapy. The most significant example is dimethylxanthenone-4-acetic acid or DMXAA [1]. Recently in our group some chiral derivatives of xanthones (CDX) exhibited interesting dose-dependent growth inhibitory effects on the evaluated human tumor cell lines and enantioselectivity in some cases [2]. In this project a library of new CDX was synthesized as single enantiomers for enantioselective studies in biological activity evaluation. The enantiomeric purity of the CDX was evaluated by liquid chromatography using chiral stationary phases. The growth inhibitory activity on three human tumor cell lines (A375-C5 melanoma, MCF-7 breast adenocarcinoma and NCI-H460 non-small cell lung) cancer was evaluated. Evaluation of COX inhibition was carried out in *in vitro* and *in silico* assays for some CDX. Regarding the evaluation of antimicrobial activity and the enantioselective studies, many compounds were evaluated and non positive results were obtained until now, but the assays will be continued. Other new CDX are being synthesized for further biological activity evaluation.

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Evaluation of antiparasitic activity of Nitazoxanide incorporated in polymeric and lipidic nanosystems

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The genus Cryptosporidium is composed of protozoan parasites that infect epithelial cells in the microvillus border of the gastrointestinal tract of all vertebrates. Found worldwide, it can be transmitted through ingestion of oocysts in contaminated water or food. Affects preferably children, being the major cause of recurrent diarrhea, and affecting immunosuppressed individuals, with a potential chronic/fatal outcome (1,2). Nitazoxanide (NTZ), the current standard treatment for cryptosporidiosis, exhibits only moderate clinical efficacy in immunocompetent individuals, and is not fully effective in patients with advanced AIDS (3). As NTZ is a poorly water soluble thiazolide derivative, nanoparticle-based drug delivery systems can be a promising strategy to deliver poorly-water soluble drug by the oral route (4).

Thus, our objective is to incorporate commercial NTZ in different nanoparticle systems (polymeric and lipidic) and verify his bioavailability and the enhancement of antiparasitic activity in vitro. It is expected that the incorporation of NTZ in nanosystems will increase drug permeability across the intestine, improve its aqueous solubility and targeting, and could be an efficient approach for the enhancement of the therapeutic index of this compound.

From proposed tasks:

1) Commercial NTZ will be incorporated in various types of nanoparticles (polymeric and lipidic)

NTZ was isolated from Alinia®tablets (Romark Pharmaceuticals) according reported methodologies (5,6). The purity of obtained NZT crystals checked by TLC, melting point and FTIR analysis. Inconclusive results regarding NZT purity indicate the need to use additional characterization methods such as HPLC.

2) In vitro cell-culture based assays are suitable for an initial screening of drug candidates, we screened different compounds for their antiparasitic activity in human colon adenocarcinoma cells (HT-29), using primed oocysts (after excystation) for cell infection and analysing cell permeability and toxicity in vitro;

Several compounds, inclusive NTZ, were tested in HT-29 cell line by MTT evaluation, with Cryptosporidium excysted oocysts.

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Monitorization of mycotoxins and heavy metals in sediments of the estuaries of the Rivers Douro and Ave.

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Mycotoxins (MT) are toxic secondary metabolites produced by fungi that colonize a variety of cereals, fruits, vegetables or can occur in food and beverages under wet conditions during storage. These compounds are of significant health concern to both humans and animals because of their carcinogenicity. The aim of this work was the monitoring of pollutants of natural origin in environmental matrices. On the previous project an analytical methodology was developed for the determination of different classes of natural pollutants such as mycotoxins (MT) in environmental matrices. This methodology was applied to the monitoring studies carried out during a year in the Douro and Ave river estuaries with seasonal sampling of water, soil and plants (spring, summer, autumn and winter). In all samples, physico-chemical parameters and the presence of metals were determined as anthropogenic indicators. In this project the anthropogenic pressure of Ave river was evaluated considering the occurrence of the selected compounds, metals and physico-chemical parameters[1]. The anthropogenic pressure of the Douro and Ave river was also evaluated considering physico-chemical parameters and trace elements distribuition [2]. To assess the spatial and temporal distribution of MT in sediment samples collected from the Douro and Ave Rivers a gas and a liquid chromatographic methods were developed and are being validated. These methods will be applied to the monitoring of several MT in sediments. Also, risk assessment and possible ecotoxicological effects of MT in sediments are being otimized by acute and chronical studies with daphnia organisms.

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New anti-Protozoa agents and aspartic peptidases as a chemotherapeutic target

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Aspartic peptidases are proteolytic enzymes present in many organisms like vertebrates, plants, fungi, protozoa and in some retroviruses such as human immunodeficiency virus (HIV). These enzymes are involved in important metabolic processes in microorganisms/virus and play major roles in infectious diseases, in the development, virulence and pathogenesis. Although few studies have been performed in order to identify and characterize aspartic peptidase in trypanosomatids, some beneficial properties of aspartic peptidase inhibitors have been described on fundamental biological events of these pathogenic agents. In this context, aspartic peptidase inhibitors used in the current chemotherapy against HIV might be able to inhibit the aspartic peptidase activity produced by different species of trypanosomatids. Furthermore, co-infections of Protozoa with HIV can potentiate the severity of these diseases by accelerating HIV replication and progression to AIDS and renders antiprotozoa treatments ineffective, often leading to relapse and patient death. Therefore, it is necessary to develop therapies and characterize new therapeutic targets to improve a more efficient treatment, specific and less toxic.

In order to accomplish for different therapeutic strategies, we found antiretrovirals effective against Leishmania and Trypanosoma parasites, namely reverse transcriptase inhibitors and protease inhibitors. Efavirenz showed the best antileishmanial activity (26.1 μM IC50) on promastigotes cells followed by delavirdine mesylate, (136.2 μM). Atazanavir exhibited the best anti-trypanosomal activity (10 μM) followed by Efavirenz (29,1 μM), Delavirdine mesylate (41,4 μM) and Darunavir (50 μM). Based on these results, we explored the activity of other active extracts and compounds, on protozoa aspartic proteases and verified that Thymol, Carvacrol and J. oxycedrus were highly effective inhibiting cathepsin D enzymatic activity of L. infantum. Aspartic peptidase of T. b. brucei was inhibited by J. oxycedrus (1 μg/mL and 3 μg/mL inhibited enzymatic activity by 50% and 85 %, respectively), as well as α-pinene (3 μg/mL inhibited 25% of enzymatic activity).

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Exploiting the potential of fish mucus

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Fish mucus displays a wide array of roles throughout fish ontogeny, from respiration, osmotic regulation, communication, locomotion and immunity. Interestingly, this multifunctional substance is yet to be economically explored despite its apparent potential. The aquatic environment is colonized by thousands of fish species, each displaying its unique repertoire of chemical defences, which can and should be investigated by the pharmaceutical industry in its continuous search for alternatives in the treatment of drug-resistant pathogens. In fact, drug resistance is a current and fundamental problem and it seems increasingly clear that the world is poised to enter a 'post-antibiotic' era. As such, in the present work, we proposed to ascertain the potential of intertidal fish mucus (a group that naturally produce massive amounts of mucus) as source/reservoir of antibiotic resistant bacteria and as an antimicrobial agent. Mucus samples were obtained from slimy fishes ('ranhosas' or 'babosas'), namely those belonging to the *Blenniidae* and *Gobiesocidae* family. The cultivable fraction of the microbiome was tested against a battery of relevant antibiotics and the levels of resistance were determined. In parallel, the antimicrobial effect of mucus was tested against several human pathogens including bacteria, fungi and protozoa. Eighty-one bacterial strains, mainly Gram negatives, were isolated from several fish species. Susceptibility (100%) was observed for aminoglycosides and quinolones in all tested isolates. Variable resistance rates were found for other antibiotics (amoxicillin: 71% resistant; amoxicillin + clavulanic acid: 70% resistant; cefotaxime: 95% resistant; imipenem: 4% resistant). It seems important to stress the high resistance levels observed for cefotaxime and the unexpected observation of resistance to imipenem, an antibiotic with application restricted to hospitals. Additionally, the preliminary results on fish mucus's antimicrobial activity are undoubtedly important and promising as at least one fish mucus sample from *L. candollei* (an elusive species in Northern Portugal) presented antimicrobial activity to several pathogenic microorganisms as *Staphylococcus aureus*, Methicillin Resistant *Staphylococcus aureus* (MRSA), *Escherichia coli* and *Candida albicans*. Curiously, *L. candollei* samples provided no bacterial isolates, an observation which further suggest this species' mucus antimicrobial activity. Ongoing work will allow us to establish the mechanisms of action behind the antimicrobial activity exhibited by this promising sample.

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Acute administration of tramadol and tapentadol induces dose-dependent toxicity in Wistar rats

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Tramadol and tapentadol are synthetic opioids prescribed for the treatment of moderate to severe pain, with low incidence of side effects. They exhibit an atypical mechanism of action, characterized by μ-opioid receptor agonism and neurotransmitter reuptake inhibition. Tapentadol has been more recently introduced into the market and is claimed to be safer than tramadol. However, the number of intoxications and fatalities associated with both opioids has been increasing along with their use. It is therefore deemed necessary to clarify the mechanisms underlying their toxicity on metabolizing and target organs.

With the present work, in vivo toxicological effects elicited by an acute exposure to tramadol and tapentadol were studied in Wistar rats.

Male Wistar rats were intraperitoneally injected with 10, 25 or 50 mg/Kg tramadol or tapentadol (corresponding to an analgesic, effective dose, an intermediate dose and the maximum recommended daily dose, respectively). Animals were sacrificed 24 hours upon administration. Serum and urine samples were collected for biochemical analysis. Brain cortex, heart, liver and kidneys were processed for the analysis of oxidative stress parameters (TBARS and protein carbonyl groups) and histopathological alterations (H&E and PAS staining).

Oxidative damage was found at the protein level for heart, liver and kidney samples. Significant lipid peroxidation was not detected. Biochemical analyses denoted dose-dependent effects, which were more pronounced for tapentadol. Results suggested potential cardiac injury (as shown by increased AST/ALT, CK-MB and lactate levels), liver dysfunction (as shown by decreased plasmatic ChE activity and urea levels), as well as kidney damage (as shown by proteinuria and decreased GFR). In turn, histological analysis evidenced signs of inflammation, cell death, vacuolization and degeneration in all tissues under study.

An acute exposure is sufficient for tramadol and tapentadol to exert toxic effects in their metabolizing and target organs, particularly when intermediate and higher doses are considered.

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Pruritus mediators in cutaneous T-cell lymphomas, mastocytosis and psoriasis

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Chronic pruritus, a major and distressing symptom, arises from a complex dialogue between skin cells and neurons, sustained by mediators, such as cytokines, neurotransmitters, endothelial adhesion molecules, angiogenic factors and others. Pruritus is a common symptom in cutaneous T cell lymphoma (CTCL), mastocytosis and psoriasis. The response to similar therapies is often different between the diseases, strengthening the need to clarify the underlying pathways and mediators involved in pruritus.

Our goal was to clarify the mechanisms underlying pruritus in CTCL, mastocytosis and psoriasis. For that, we measured different cytokines (IL-8, IL-31 and IL-33), neuromediators (serotonin), endothelial adhesion molecules (E-selectin) and angiogenic factors (VEGF) in these patients; the correlation of biomarkers with itching score and disease severity was studied.

We found that CTCL patients presented increased IL-31 and E-selectin levels, especially patients with Sezary Syndrome (SS); E-selectin correlated with pruritus in SS. In Mycosis Fungoides (MF) serotonin presented a tendency for higher levels. Pruritus correlated with tryptase in mastocytosis. Although we found elevated IL-8, E-selectin, VEGF and CRP levels in psoriasis, they did not correlate with pruritus.

Our data suggest that serotonin and tryptase are important biomarkers in mastocytosis; E-selectin and CRP are potential biomarkers of psoriasis severity; in SS patients, E-selectin and IL-31 appear to be important in itchy pathways; in MF he increase in serotonin seems to be more important in the mechanisms underlying pruritus.

Our data strengthens the hypothesis that different mechanisms underlie the genesis of itch, explaining the different therapeutic responses to common treatments, and proposes some potential therapeutic targets for the treatment of itch in CTCL, mastocytosis and psoriasis patients.

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The mitotic protein Spindly as a cancer therapeutic target

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Microtubule-targeting agents (MTAs) such as paclitaxel are used extensively for the treatment of diverse types of cancer. They block cancer cells in mitosis through the activation of the spindle assembly checkpoint (SAC), the surveillance mechanism that ensures accurate chromosome segregation at the onset of anaphase. However, the cytotoxic activity of MTAs is limited by premature mitotic exit (mitotic slippage) due to SAC silencing. Here we have explored the dual role of the protein Spindly in chromosome attachments and SAC silencing to analyze the consequences of its depletion on the viability of tumor cells treated with clinically relevant doses of paclitaxel. As expected, siRNA-mediated Spindly suppression induced chromosome misalignment and accumulation of cells in mitosis. Remarkably, these cells were more sensitive to low-doses of paclitaxel. Sensitization was due to an increase in the length of mitotic arrest and high frequency of aneuploidy, both correlated with an exacerbated post-mitotic cell death response as determined by cell fate profiling. Thus, by affecting both SAC silencing and chromosome attachment, Spindly targeting offers a double-edged sword that potentiates tumor cell killing by clinically relevant doses of paclitaxel, providing a rationale for combination chemotherapy against cancer.

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Biomarkers on potential malignant disorders and oral squamous cell carcinomas

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Unravelling the molecular mechanisms underlying metabolic modulators inhibition of tumor progression and treatment resistance

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Tumour cells exhibit a reprogrammed metabolism, relying mainly on glycolysis for energy production, even in the presence of normal oxygen levels, instead of oxidative phosphorylation (OXPHOS). This altered metabolism enhances tumour aggressiveness characteristics such as cell proliferation, metastization, and resistance to therapy. The differences in metabolism between normal and cancer tissues are considered the Achilles heel of cancer and offer a powerful opportunity for new cancer therapy strategies. In this way, novel compounds directed to this phenotype have emerged in recent years, aiming at more specific and effective cancer treatment.

The aim of this study was to understand the role of metabolic modulation in tumorogenesis of glioma and breast cancer cells. For that we used metabolic modulators targeting different energetic pathways, namely 3-bromopyruvate, 2-deoxyglucose, dichloroacetate (DCA) (all glycolytic inhibitors). The effect of these compounds was evaluated in some metabolic parameters. We also assessed the effect of these compounds combined with conventional antitumor drugs.

Our results clearly show that cells treated with the energetic modulators present a decrease in cell viability and an altered metabolic profile in most cases. There was a decrease in glucose consumption and consequently a decrease in lactate and ATP production rates, when the cells were treated with the glycolytic inhibitors. Additionally, pre-treatment of cells with these bioenergetic modulators effectively enhanced, even for lower concentrations, the cytotoxicity of conventional antitumor drugs in all cases.

Aiming to unravel the molecular mechanisms underlying the metabolic modulators action, a 3-BP resistant cell line, derived from the breast cancer cell line ZR-75-1 cell line, previously characterized as sensitive to 3-BP, was also created. After approximately 12 months, ZR-75-1-R cells were obtained, with a final resistance index of 4, relatively to the respective sensitive parental cell line (ZR-75-1-S). It has been found that ZR-75-1-R and ZR-75-1-S cells presented several differences in basal conditions, as well as in their response to 3-BP and to other antitumor drugs.

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Bioengineered FcRn-targeting nanoparticles for intestinal delivery of biopharmaceuticals

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Insulin encapsulated polymeric nanoparticles were produced, targeting the FcRn by functionalization with wildtype (wt) and two variant (var) albumins. Insulin encapsulated nanoparticles produced in a batch size of 20mg polymer were used to produce bare NPs, resulting in a mean size, PDI, zeta potential of 204 nm, 0.094 and -5.1 mV for no-functionalized NPs respective sizes of 220, 306 and 330 nm, PDI of 0.105, 0.247 and 0.275 and respective zeta potentials of -4.5, -4.3 and -4.4 mV for NPs functionalized with wt albumin, variant albumin K500A respective K573P. The albumin association efficiency of these NPs, indirectly determined by BCA assay, was 42%, 50%, respective 79% for unfunctionalized NPs, NPs functionalized with wt albumin, variant albumin K500A respective K573P. Functionalized NPs were then used for in vitro cellular binding/internalization assays using the human colon carcinoma cell line Caco2. Cells for FACS have been incubated with NPs at pH 6 and pH 7.4, whereas for the Imaging Flow Cytometry experiment cells have been incubated only at pH 6. In both assays it was able to show a specific binding of functionalized NPs towards the FcRn, whereas a pH dependent binding/internalization of particles to the cells was able to be proven. Moreover an FcRn binding ELISA at pH 6 was performed of those NPs, proofing a significantly higher binding affinity of K573P-functionalized NPs towards the receptor compared to the wildtype- respective K500A-functionalized NPs

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Development of lipid-based particle for the encapsulation of dietary bioactives

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Research and application of dietary bioactives are areas of great interest in the functional foods, nutraceutical and pharmaceutical industries due to their potential health benefits. Bioactive dietary components can be divided into bioactive molecules, such as polyphenols, and bioactive living cells (probiotics). Both bioactive molecules and bioactive living cells may benefit from encapsulation since many report low bioactivity due to adverse effects of (i) processing and storage in the products that serve as vehicles and due to (ii) deleterious circumstances during transport through the gastrointestinal tract [1]. Encapsulation may increase not only stability and/or viability but also functionality, and may facilitate targeted release in specific parts of the gut. However, despite the fact that several delivery systems have been proposed over the years the application of food delivery systems to realistic food products is still considered to be in its infancy [2].

The main objective of this project was to develop novel food-grade lipid-based delivery systems able to protect probiotics. Encapsulation with lipid matrices is promising because lipids are likely to stabilise probiotics by protecting cells against storage stress, and possibly blocking them from exposure to water and stressors, such as H^+ ions [3]. However, there are still limited reports on the successful encapsulation of probiotics in lipid-based coating materials. The multiple (w/o/w) emulsion process described by Fangueiro et al. [4], using cocoa butter and Dynasan 114 was chosen for this study. However, it appears that this method, under the conditions studied, is not suitable for the encapsulation of bacteria as low encapsulation yields (< 10%) were obtained.

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Hepatic effects of Long-term Tamoxifen Administration to Cycling Female Rats

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International guidelines recommend the use of tamoxifen (TAM) as preventive treatment in healthy premenopausal women (age 30-35 years) with high-risk of breast cancer [1]. However, the benefit-risk ratio of this preventive intervention needs to be better understood. This drug is a non-steroid estrogen receptor (ER) modulator [1] that may either facilitate or block ER-mediated responses depending on organ or tissue types [2]. TAM can induce changes in body weight and affect metabolic homeostasis including glucose and lipid metabolism, inducing liver injury and causing hepatic steatosis in patients with breast cancer [3-4]. Given the paucity of the effects of long-term TAM therapy in young premenopausal women, an animal model of long-term TAM administration to cycling adult female rats was developed to evaluate its effects on liver histopathology. Young adult cycling female rats were given 5 mg/kg bw of TAM, p.o., every day for three-months. Body weight and food consumption were monitored. Liver samples were processed for light microscopy and 3 µm thick sections were stained with hematoxilin-eosin (HE) and periodic acid-Schiff (PAS). Other liver samples were frozen in liquid nitrogen, embedded in Tissue-Tek, cryosectioned at 4 µm thick, stained with Oil Red O (ORO) and used to determine the percentage of fat inclusions in hepatocytes using an image analysis system. The body weight was significantly lower in TAM treated rats after 3 months of treatment, when compared with the control group. In PAS sections and ORO sections of TAM-treated rats, lower glycogen storage close to the portal areas and high percentage of area occupied by lipid droplets was observed in hepatocytes when compared with sections of control rats, respectively. These morphological data are in accordance with previous studies suggesting an inhibition of gluconeogenesis and a stimulation of glycolysis [5], as well as the incidence of fatty liver upon TAM therapy [4].

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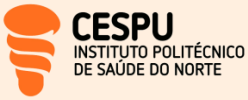
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