DAY 2

Pharmaceutics & Drug Delivery Systems

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Poster Presentations

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Enhancement in mitochondrial biogenesis by (-)-epigallocatechin gallate (EGCG) through conjugation with a methyl-branched carbonate chain

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(-)-Epigallocatechin-3-gallate (EGCG) is known as a mitochondria-targeted molecule that can prevent mitochondrial deterioration and induce mitochondrial biogenesis by modulating key regulators of mitochondrial metabolism. In this study, we tackled whether derivatization of EGCG could result in enhancement of its effects on mitochondrial biogenesis. EGCG, EGCG peracetate (AcEGCG), and its 4"-O-alkyl substituted congeners prepared by previously reported procedures were biologically evaluated. Interestingly, EGCG and AcEGCG were only marginally effective in inducing mitochondrial biogenesis, while AcEGCG congeners with an alkyl group at the 4"-O position showed significantly increased biological activity compared to their parent compound. Among these series, compound 3f with a methyl-branched carbonate chain at the 4"-O position of the AcEGCG scaffold showed the most enhancements in inducing mitochondrial biogenesis. Hepa1-6 cells treated with 3f exhibited increases in both mitochondrial mass (1.5 times) and relative mtDNA content to nDNA (1.5 times). As a mitochondrial biogenesis enhancer, 3f also increased expression levels of regulators for mitochondrial function, including PGC-1 α (4.0 fold), p-AMPK (2.5 fold), SIRT1 (4.2 fold), ERR α (1.8 fold), NRF-1 (1.6 fold), NRF-2 (1.7 fold), and mtTFA (2.0 folds). Investigation of oxidative phosphorylation by mitochondria in the presence of 3f revealed that 3f increased NAD+/ NADH ratio, the amount of cytochrome C, ATP synthesis, and oxygen consumption in Hepa1-6 cells by 2.2, 1.4, 1.5, and 2.1 folds, respectively. Taken together, these results warrant extensive structure-activity relationship study for EGCG derivatives to develop novel mitochondrial biogenesis enhancers.

Biography

Youhoon Chong has completed his PhD from University of Georgia, and Post-doctoral studies from The Scripps Research Institute. He is the Chairman of the Department of Integrative Bioscience and Biotechnology, Konkuk University. He has published more than 140 papers in reputed journals.

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Therapeutic protein-only nanoparticles as targeted antitumoral drugs

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Nowadays, conventional cancer treatments present high systemic toxicity, leading to side effects on healthy tissues. For that reason, it is of great relevance to develop targeted drugs that can increase the local drug concentration, minimize toxic effects on off-target tissues and reduce the dose administered. Moreover, loading capacity and drug leakage from vehicles during circulation in blood is a major concern when developing nanoparticle-based cell-targeted cytotoxics. To circumvent this potential issue, it would be convenient the engineering of drugs as self-delivered nanoscale entities, devoid of any heterologous carriers. In this context, we have engineered potent protein toxins, using the active fragments of the diphtheria toxin and the Pseudomonas aeruginosa exotoxin, as self-assembling, self-delivered therapeutic materials targeted to CXCR4⁺ cancer stem cells. CXCR4 receptor is overexpressed in a variety of human cancers and plays a critical role in metastatic process. For this reason, we have fused T22 to the toxic domains (T22-TOXIN-H6), as it is a CXCR4 ligand able to bind specifically and internalize into the target cells. The systemic administration of both nanostructured drugs in a colorectal cancer xenograft mouse model promotes efficient and specific local destruction of target tumor tissues and a significant reduction of the tumor volume. This observation strongly supports the concept of intrinsically functional protein nanoparticles, which having a dual role as drug and carrier, are designed to be administered without the assistance of heterologous vehicles. The promising results obtained have allowed the development of a new patent (EP17169722) that has been licensed to Nanoligent SL.

Biography

Laura Sánchez García is a PhD student at the Universitat Autònoma de Barcelona, Spain. She is doing her research in the Nanobiotechnology Group, which is working in the development of targeted protein-only nanoparticles against cancer stem cells. She has studied her degree in Microbiology and Master's in Applied Microbiology. She has published 13 papers in reputed journals and has received an EMBO Fellowship to perform a three-month internship in Slovenia.

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Enhanced immunity in intradermal vaccination by novel hollow microneedles

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Background & Objective: We have developed a new device with multiple fine needles fabricated with a bevel angle to release a drug broadly and homogeneously into the skin in a horizontal fashion and reported in the article. It led us to develop another type of multiple needles to release a drug in the epidermis or upper dermis. The intradermal (ID) route for vaccination represents an effective alternative to subcutaneous (SC)/intramuscular administration to induce protective immunity. However, a critical issue associated with ID vaccination is the precise delivery of solution in the upper dermis, which ensures enhanced immunity.

Methods: We fabricated a hollow microneedle unit made of poly-glycolic acid by injection molding and bonding and developed a dedicated prototype injector. To ensure ID delivery of solution, the injected site was macroscopically and microscopically examined. Serum immunoglobulin G antibody production was measured by enzyme immunoassay and compared in groups of rats following either ID delivery with microneedles or SC administration with a 27-G stainless needle of graded vaccine doses.

Results: The unit used a tandem array of six microneedles, each with a side delivery hole, and a conduit inside for solution. Microneedles installed in the injector punctured at the skin with the aid of a spring. Injection of solution formed a wheal due to ID distribution. Histologically, a wedge-shaped skin defect in the upper skin corresponded to each puncture site. Antibody titers following vaccinations on days one and eight were significantly higher with ID injection than with SC delivery on day 15 and every seven days, thereafter until day 36 with mumps vaccination, and until day 36 with varicella vaccination.

Conclusions: The microneedle unit presented here delivered solution intradermally without any difficulty and evoked antibody responses against viruses even with the reduced vaccine volume. Our findings confirm promising results of ID delivery as an immunogenic option to enhance vaccination efficacy.

Biography

Hidekazu Fukamizu is the Director of Department of Plastic and Reconstructive Surgery, Hamamatsu University School of Medicine. He published few articles on drug delivery in the following journals: "Development of three-microneedle device for hypodermic drug delivery and clinical application" in Plastic and Reconstructive Surgery, 2012; "Application of a three-microneedle device for the delivery of local anesthetics" in Patient Preference and Adherence, 2015.

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Rheological approach to develop new mucoadhesive spray formulations

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Mucoadhesion describes the attractive forces between a material and mucous membranes. Mucoadhesive formulations are designed to form specific interactions with mucosal membranes, providing localized drug release, prolonging residence time, reducing dosing frequency and increasing patient compliance.

The aim of this project was to select the better performing polymer to develop a new mucoadhesive spray formulation, containing an anti-inflammatory drug, using a rheological approach. Hassan and Gallo rheological synergism method was chosen. This method is based on the idea that when a mucoadhesive polymer is mixed with mucin, there is a synergistic increase in viscosity. Commercial oral sprays (medical devices), claiming a mucoadhesive effect on the leaflet, were used to assess the method validity and to identify formulation viscosity values compatible with a spray device.

Prototype spray formulations, containing different known mucoadhesive polymers, were prepared. The influence of polymer type and concentration on formulation bioadhesive properties was tested. Formulation prototypes were subjected to prestability studies at 4°C, 25°C and 40°C for 1 month (in absence of preservatives). A spraying test was used to investigate the polymer influence on the ability of the device to spray, even in the case of a discontinuous use over time.

All formulations resulted to be physically stable at all temperatures. The mucoadhesive properties changed significantly depending on the polymer type and concentration. Prototypes containing sodium alginate as mucoadhesive agent showed the highest mucoadhesion properties, due to its ability to gel in the presence of Ca^{2+} ions of salivary fluid, which results in a rise in viscosity.

Biography

Leonardo Marchitto is a Vice President of the School of Pharmacy, Biotechnology in university of bologna, Italy. He completed his Master Degree in Industrial Pharmacy (University of Pavia), and Degree: Pharmacy (University of Camerino)

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Ethiopian folk medicine for treatment of anti-rabies: A review

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Background: Rabies is a serious disease caused by a virus, mainly zoonotic which affects warm blooded animals. The dog is the species most responsible for human exposure, with 98% of human case and vaccination due to the bite rabid or suspected rabid dogs.

Objective: The objective of this study was to identify, document, asses the route of administration and preparation methods of medicinal plants used for anti-rabies.

Method: Ethnobotanical data review was conducted on published article for medicinal plants for treatment of rabies in Ethiopia from Google scholar, pub med, thesis dissertations and unpublished thesis reports. Data analysis was conducted using excel. Rabies, anti-rabies, medicinal plants, Ethiopia were the search terms used.

Results: Thirty-seven plant species which belong to 17 families were found to be used in the treatment of anti-rabies in Ethiopia from the data review. Euphorbiaceae, Phytolaccaceae, Fabaceae and Cucurbitaceae were the most commonly used families respectively, whereas Phytolacca dodecandra L and Ricinus communis L were the most used plant species. The habit forms of the plant species were shrubs 37.83% and herbs 13.5% while the most commonly used parts of the plant were 56.75% roots and 21.6% leaf are used. The route of administration and preparation of those medicinal plants were crushed dried root and mixed with water and given with tef kita.

Conclusion: Phytolacca dodecandra L and Ricinus communis L were the most used traditional folk medicine for rabies treatments. Oral preparation is the most common administration of medicinal plants. It is recommended to perform phytochemical screening for most reported plants.

Biography

Hiwot Moges Bekele is a Pharmacist and a Researcher on traditional and modern medicine research directorate, at Ethiopian Public Health Institute. Currently, she is involved in many research projects such as national survey on traditional medicine of Ethiopia, anti-malaria, anti-helminthic. Also, she is finalizing her Master's degree on Pharmacoepidemiology and Social Pharmacy.

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Accepted Abstracts

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NIR and Raman spectroscopy in quantification of three API's in solid pharmaceutical preparation

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The pharmaceuticals manufacture is one of the most regulated industrial sectors, these regulations require a high number of physical and chemical determinations. Techniques such as near infrared spectroscopy and Raman spectroscopy are being widely used in the pharmaceutical industry. The principal advantage of this technique is the possibility of obtaining information without sample preparation, and the possibility of analyzing samples in different matrices. The aim of the present study was, to develop a NIR and Raman method to determine the active content of three API's (6.8% w/w, 25% w/w and 25% w/w). Different spectral pretreatments were used for reducing spectral variabilities associated to physical characteristics of the samples. SNV was used to reduce scattering effects and second derivative treatment in combination with second polynomial Savitzky-Golay data point was used for normalization and baseline correction. Each model was developed with full subsets cross-validation and external validation (industrial and laboratory-made samples). Several prediction models were performed with various parameters and the best model was selected based on conventional criteria, R2, RMSECV, RMSEP among others. Finally, no significant differences were found between the NIR and Raman prediction and HPLC reference data of the validation and industrial samples, and the analytical parameters evaluated were within the stipulated margins. In addition, Raman spectroscopy, was possible to detect problems with the homogeneity of the active ingredients in the pharmaceutical product, which helped to improve the laboratory practices of the pharmaceutical industry.

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Evaluation of the residence time during dry, wet and hot melt granulation

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win screw extrusion offers a promising method to continuously process and transform physicochemical properties of L pharmaceuticals and excipients and produce tailored products given its accurate control of process parameters. Certainly, one of the strengths of continuous manufacturing is the consistency in maintaining a certain product quality. In order to maintain such consistency, it is necessary to process feed materials for an optimized controllable time, also known as the residence time. The residence time is a parameter characterizing the duration for a single particle to partake in the extrusion process. As a result, the residence time and its associated distribution are parameters highly affecting the quality of output products. Additionally, if an existing process is desired to be scaled up or a process transfer scheduled to an extruder with different geometries, evaluation and comparison of residence times of both processes will be useful given its relative ease of measurement. As the residence time is a result of mass flow and mixing patterns within the extruder, it is highly dependent on process variables, such as feeder flowrate, extruder screw design and configuration and material properties. The purpose of the present study is to, study the effects of the feeder input mass flowrate on the residence time distribution and to investigate the effects of material properties on the residence time by investigating different materials under the same processing conditions during wet granulation and hot melt extrusion (HME). Based on experimental data obtained from residence time distribution curves for wet and dry granulation, at steady state it appears that the feeder flowrate plays significant role in the residence time distribution obtained but the degree of influence is strongly dependent on the rotation speed of the extruder and the material properties. Positive changes in peak height and negative changes in residence times are observed with an increase in feeder flowrate.

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Targeted pharmacological regulation of intracellular signal transduction in regenerative-competent cells: A new direction of therapy in regenerative medicine

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Advances in the field of cellular technologies have led to the possibility of developing a new direction of targeted therapy in regenerative medicine - Strategy of pharmacological regulation of intracellular signal transduction in regenerator-competent cells. The role of NF-κB, IKK, PKC, PKB, PI3K, ERK½, p38, adenylate cyclase, PKA, JAKs, STAT3, JNK and p53 in the realization of functioning progenitor elements of different classes and cells of tissue microenvironment was studied in vitro by means of cultural, immunological and the other methods. On the models of post hypoxic encephalopathy, skin wound and cytostatic myelosuppression in experimental animals the therapeutic effects and mechanisms of action of modifiers of signal molecules activity were studied. The specificity of the involvement of several signaling molecules in the regulation of cell cycle and development of progenitor cells of Various classes, as well as in the production of neural stem cells of brain were shown on the model of encephalopathy. An algorithm and approaches for estimating the potential efficiency and many-sided selectivity of the modifiers of signaling molecules activity as targeted hemostimulators were developed. The effectiveness of various targeted pharmacological agents determined by the selective effect on different types of regenerative-competent cells was demonstrated on the models of cytostatic myelosuppression of various genesis. The perspective of using intracellular signaling molecules in regenerative-competent cells as targets of drugs for regenerative medicine was shown.

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Towards the elaboration of BODIPY-gold(I) theranostics for medical applications

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Since the pioneer discovery of cisplatin for biological applications by Rosenberg in the 1960's, metal complexes have become the most currently investigated and used class of compounds in cancer chemotherapy. Gold-based derivatives gave very promising results as anticancer agents. One challenging question is to understand their mechanism of action in order to improve the efficiency while limiting their side effects. One elegant way to manage this issue consists in attaching a fluorophore on the complexes to be able to track them in vitro. Thus, we recently developed three metal-containing BODIPY-phosphine compounds based on Ru(II), Os(II) and Au(I). This first series of complexes showed promising results: interesting IC50 in several cancer cell lines, especially for the Au derivative. Additionally, we succeeded in following the compounds in vitro by optical imaging. In a second part, we decided to modify the physicochemical properties of gold(I) complex for it to be suitable for in vivo studies in small animals. First, the absorption and emission wavelengths of the compounds were shifted to the near infrared region (in the "therapeutic window") by extension of the conjugation of the BODIPY core. In parallel, we investigated the possibility to introduce small biovectors on the gold center for targeting selectively cancer cells. The synthesis and the photophysical studies, and the biological studies of the different targeted systems will be presented and discussed.

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Applications of supercritical fluids in the pharmaceutical industry

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The advantageous and tunable properties of supercritical fluids being high densities, high diffusivities, low viscosities and near zero surface tension, make them unique and applicable in many areas. In this presentation, new promising applications of supercritical carbon dioxide in the pharmaceutical industry will be demonstrated, with the focus on the development of novel drug delivery systems. Besides incorporation of drugs into polymers and composites, supercritical fluid applications offer possibilities of tailoring the properties of the final product (e.g., pore size distribution), control of the active substance loading and consequently obtaining diverse drug release kinetics. Examples of development of polymer-based materials for the controlled release of active components by supercritical solvent impregnation of solid dispersions of drugs in polymers by processing with supercritical carbon dioxide will be presented. A brief overview of other applications of interest for the pharmaceutical industry, like fractionation of natural bioactive components, particle design and drug formulation will be provided as well.

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Captopril ameliorates L-arginine induced acute pancreatitis via downregulation of iNOS and elevation of glutathione

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A cute pancreatitis (AP) is a common inflammatory disease mediated by damage in acinar cells and subsequent pancreatic inflammation with infiltration of leukocytes. The pancreatic renin-angiotensin system may play an important role in the pathogenesis of AP. The present study aimed to investigate the possible role of captopril (CAP), an angiotensin-converting enzyme inhibitor, in attenuating L-arginine-induced AP in a rat model and to elucidate the underlying molecular mechanisms. Forty-eight adult male Wister rats were divided into four equal groups: control group (rats received vehicle orally for 10 days), AP group (3 g/kg L-arginine, single i.p.) on 10th day of the experiment, CAP group (50 mg/kg captopril, orally, once daily) and MP group (30 mg/kg methylprednisolone, orally, once daily). CAP and MP were administered for 10 days prior to L-arginine injection. Then rats were sacrificed 24 hours after L-arginine injection. Inflammatory biomarkers; pancreatic tumor necrosis factor-alpha (TNF- α) concentration, myeloperoxidase (MPO) activity and inducible nitric oxide synthase (iNOS) gene expression were determined. Oxidative stress biomarkers; nitric oxide (NO) and reduced glutathione (GSH) concentrations were assayed. In addition, serum α -amylase and lipase activities were measured and histopathological studies of the pancreas were done. CAP treatment significantly reduced TNF- α , MPO activity, NO and downregulated iNOS gene expression compared to AP group. CAP treatment significantly, increased pancreatic GSH and ameliorated the histological changes of AP. Captopril treatment may have a protective role in AP rat model which is comparable to MP treatment.

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Baicalein attenuates LPS-induced oxidative stress and inflammation, might be via CaMKII inhibition

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Oxidative stress and inflammation are two major contributing factors to most chronic diseases including cancer, diabetes, cardiovascular, neurological and pulmonary diseases. Baicalein, a flavonoid bioactive compound from Scutellaria baicalensis Georgi (also known Scutellaria Radix or Huang Qin), has demonstrated antioxidant and anti-inflammatory potentials. However, the indepth mechanistic studies on this compound with protective effects remain to be discovered. This study on lipopolysaccharide (LPS)-induced reactive oxygen species (ROS) in macrophages showed that pre-treatment with baicalein significantly attenuated oxidative stress by reducing the ROS levels in a dose-dependent manner (0.1 μ M, 0.33 μ M, 1 μ M, 3.3 μ M and 10 μ M). The antioxidant effects of baicalein were 100 times stronger than N-Acetylcysteine (NAC), a commercial antioxidant agent. Furthermore, the antioxidant effects of baicalein showed the same inhibitory pattern with KN-93, a specific inhibitor of CaMKII, in the LPS-induced ROS production in vitro. Moreover, pre-treatment of baicalein also significantly decreases LPS-induced inflammation in macrophages by reducing the pro-inflammatory mediators, including IL-6, monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein -1(MIP-1), regulated on activation in normal T-cell expressed and secreted (RANTES) and tumor necrosis factor (TNF α) in a dose-dependent manner as well. We are currently identifying if CaMKII (Ca²⁺/calmodulin-dependent protein kinase II) would be a potential primary target by baicalein with utilizing small-molecule affinity purification, and if the decreased oxidative stress which could lead to the reduced inflammation by baicalein's inhibition of CaMKII involves the attenuation of p38MAPK and JNK signaling pathway for LPS-induced cytokine production by macrophage.

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Dendrimer-based drug delivery system- focus on Indian visceral leishmaniasis

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Leishmaniasis: a vector-borne disease has a worldwide existence. It presents mainly in four forms: visceral leishmaniasis, cutaneous leishmaniasis and post kala-azar dermal leishmaniasis (PKDL). In India, visceral leishmaniasis is the most existence type of leishmaniasis. Visceral leishmaniasis is also known as kala-azar, black fever, dumdum fever, burdwan fever, sarkari bimari etc. Visceral leishmaniasis is caused by Protozoa species haemoflagellate Leishmaniasis donovani and transmitted by the bite of sand flies of Phlebotomus genus. Visceral leishmaniasis affects various age groups. Approximately, 10 k morbidity with 1 k mortality occurs annually due to visceral leishmaniasis in India. Fast urbanization, poverty, improper sanitation, lack of knowledge about prevention and individual risk factors like HIV, malnutrition and genetic susceptibility is the major source of visceral leishmaniasis existence in India. Approximately, 90% cases of Indian visceral leishmaniasis come from Bihar. Available treatment modalities have limitations like serious side effects, nonoral solubility, high cost and long hospitalization, due to this, a favorable treatment option for visceral leishmaniasis is still out of range of a common man. A dendrimer is a new generation of artificial polymeric macromolecules constructed in a step-by-step fashion using repetitive chemistry. Dendrimer has a number of applications in several pharmaceutical fields such as enhancing the solubility of the poorly soluble drug, enhancing the delivery of DNA, and as a carrier for the development of novel drug delivery systems. The present research emphasizes the development of a conjugate of dendrimer with the nonoral soluble drug for the purpose of oral solubility enhancement and then use for the treatment of visceral leishmaniasis.

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