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TARGETING GLUCOCORTICOID RECEPTOR: A POTENT DRUG-SENSITIZING, NANO-THERAPEUTIC DELIVERY STRATEGY FOR CANCER

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Abstract:

As glucocorticoid receptor (GR) is ubiquitously expressed in cellular cytoplasm in almost all cells, cancer or non-cancer, it is a logically unsuitable receptor candidate for targeting cancer. This nuclear hormone receptor, and its activation/ transactivation/ deactivation profile by its interaction with cognate ligands, i.e., glucocorticoids are well known and well studied in various physiological & pathophysiological conditions including inflammation, immune function, development etc. Moreover, GR induces gluconeogenesis, the alternate pathway to produce energy inducing carbohydrate, i.e., glucose using non-carbohydrate precursors. Thus it contributes to overall horizon of cellular energy metabolism and acts as stop-gap mechanism to produce energy especially during starvation-like crisis. But, cancer cells love to undergo glycolysis over gluconeogenesis because glycolysis is energetically preferred. So, may we say that selectively instigating gluconeogenesis over glycolysis in cancer cells, or in other words, selectively instigating the related receptor, i.e., GR could be a potential avenue to develop anticancer therapeutics? Is GR waiting to be discovered as a new target for cancer? In this regard, using multi-prong approaches over last 12 years we established that GR is indeed a potential target for cancer. We discovered that GR in cancer cells are functionally different than the GRs of non-cancer cells by an enigmatic, yet inexplicable compromising role of cancer cell-associated HSP90 [1-2]. This cancer cell-associated aberration of GR can be manipulated by unique lipid-based as well as gold nanoparticle-based formulations to instigate reversal of drug resistance, de-differentiation and reversal of epithelial to mesenchymal transition (EMT) in cancer stem cells and in aggressive tumours [3-6]. Following these, we

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witnessed unprecedented levels of drug-sensitivity in cancer cells against multiple drugs to which it had become resistant previously. We are projecting these GR-targeted nanoformulations as a unique platform technology for repurposing multiple drugs in cancer to treat most, if not all phenotypes of cancer.

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CATIONIC NANOSIZED EMULSION TECHNOLOGY FROM BENCH TO PATIENTS

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Abstract:

Background: Conventional contrived solutions (tear substitutes) require frequent instillation into eyes to correct or treat dry-eye syndrome. Oily eye drops are also not acceptable to patient due to visual disturbance following instillation of oily drops into eyes (Lallemand et al 2003). Since the ocular surface tissues such as cornea and conjunctiva are negatively-charged at physiological pH (Rojanasakul and Robinson 1989), the drug delivery carriers with positive global charge might be of useful for undergoing an interaction with the ocular surface tissues via electrostatic forces to improve the drug ocular pharmacokinetic parameters and thus its efficacy. To minimize dosing frequency and ocular disturbances problems associated with eye drops, the peptidic cyclosporine A (CsA) is incorporated into oil-in-water nanosized emulsions and the ocular pharmacokinetics, irritation potential as well as safety are being assessed before marketing the CsA-loaded emulsions.

Objectives: The objectives of this study are (1) to find a suitable oil or oil combination for dissolving the adequate amount of CsA, (2) to select the appropriate cation-conferring emulsifier molecules, (3) to characterize the CsA-loaded cationic emulsions (particle size zeta potential, drug content, stability, etc.), (4) to perform comparative ocular pharmacokinetic study of CsA-loaded anionic and cationic nanosized emulsions using contralateral and treated eyes of rabbit, (5) to assess ocular irritation potential of applied CsA-loaded cationic emulsions in long-and short-time ocular toxicity experiments and (6) to position successfully the CsA-loaded cationic emulsion into the market for correcting or treating the dry-eye syndrome.

Methods: A step-wise emulsion preparation method involving both low-and high-energy equipments were used to make nanosized emulsions. Traditional

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methods to assess the drug content, particle size distribution, irritation potential via Draize scoring, etc. were applied onto the CsA-loaded emulsions. The CsA accumulation into the different ocular tissues at different post-instillation time periods were also assessed via radiolabeling assay method.

Results & Discussions: The CsA amount in cornea and conjunctiva tissues (in terms of AUC values) were found to significantly high (2.3 and 1.8 times, respectively) when the drug is incorporated into the cationic emulsion rather than anionic counterpart. This result indicates that the occurrence of electrostatic forces between the cationic oil droplets of the emulsion and anionic ocular tissues. Furthermore the retention of therapeutic amount of CsA even after 8 hour post-instillation time period signifies the possible reservoir type of activity produced by the cationic emulsion to correct or treat the dry-eye syndrome.

Conclusions: The CsA-loaded cationic emulsion showed improved ocular pharmacokinetics in comparison to CsA-loaded anionic emulsion. Although the CsA-loaded cationic emulsion can stable for 90 days at 24° C, the possibility of making solid-dry powder for reconstitution for topical eye drops is currently under investigation at our laboratory in NIPER-Guwahati through DBT-sponsored research project.

Keywords: *Dry-eye syndrome, cyclosporine A, oil-in-water nanosized emulsion, cornea, conjunctiva*

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PURSUING SCIENCE AT THE NANOSCALE FOR POTENTIAL NANOBIOTECHNOLOGY

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Abstract:

We utilize of the optical, magnetic, photothermal and chemical properties of nanoscale particles for applications in healthcare [1]. The nanoscale particles usually consist of metal atom clusters, quantum dots and metal or iron oxide nanoparticles. On the other hand, we are currently trying to develop strategies for fabricating multifunctional nanoscale structures for theranostics [2] Here we put together metal clusters, nanoparticles, biopolymers and marketed drugs for model drug delivery, imaging and magnetic targeting [3-5]. The idea of synergy of action of the components is also part of the strategy.

We also work on potential real life applications of the materials and develop appropriate technology in this regard. For example, I will talk about a "thumb imprint" based device for diagnosis of hyperbilirubinemia (jaundice). Here the luminescence of Au atomic clusters serve as a visual marker for jaundice. The simple process of fabrication and portable nature of the device make it convenient to probe excess bilirubin deposited on skin of the afflicted patients [6,7]. Further, a device for use in gene and protein analyses on a single platform, with the Au nanoclusters as the signal generating agent, has been developed [8,9]. We are also interested in developing devices for biochemical assays.

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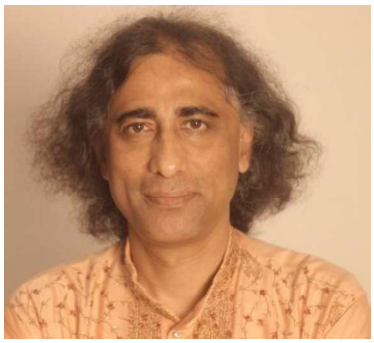

Dr. Arun Chattopadhyay is a Professor of the Department of Chemistry at the Indian Institute of Technology Guwahati. He has been the founder Head of the Centre for Nanotechnology (2004-2009) and Head of Chemistry from 2009-2014. Prof. Chattopadhyay obtained his M. Sc. in Chemistry from the Indian Institute of Technology Kanpur (1988) and PhD in Chemical Physics from Columbia University (New York) in the year 1992. He then went on to pursue postdoctoral work at Stanford University (1992-1995).

He received Swarnajyanti Fellowship Award (2003-2004) of the Department of Science and Technology, Government of India; Materials Research Society of India Medal (2008) and Young Career Award in Nano Science and Technology (2013), DST (Nano Mission). Prof. Chattopadhyay has been elected to be the Fellow of the Indian Academy of Sciences (2016), Bangalore and Fellow of the Royal Society of Chemistry (2014).

Dr. Chattopadhyay leads a group of research workers carrying out research in the frontier areas of nanoscale science and technology. His group invented the concept of submicron-scale lithography in color, introduced the concept of one-pot synthesis of nanocomposite and complexation reactions on the surface of quantum dots and involving atomic clusters. He also pioneered the spectroscopy of individual soap bubbles. He has made original contributions in nanobiotechnology. Recently his group has submitted patents on the thumb imprint based detection of hyperbilirubinemia and a nanotechnology based portable machine for pursuing gene and protein analyses. An important area of his current research is assembly of nanoscale particles in one, two and three dimensions. His group has been able to make important contributions in that direction.

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CATIONIC LIPID CONJUGATES OF NUCLEAR HORMONES AND VITAMINS: A NEW CONCEPT IN ANTICANCER THERAPY & NANOTECHNOLOGY

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Abstract:

Hormones or synthetic ligands of nuclear hormone receptors (NHR) play major roles in modulating transactivation pattern of these receptors, thereby promoting/regulating the expression of various factors. Estrogen, the natural hormone for estrogen receptor (ER) plays a major role in promoting hormone responsive breast cancer. The presentation will first showcase how cationic lipid modification/conjugation to estrogen changes its activity pattern. It acts against all kinds of breast cancer cells irrespective of their ER expression status. The molecule brings havoc by prompting simultaneous autophagy and apoptosis in breast cancer cells [1-2]. We extended this strategy to ligands targeted to other NHRs [3], sigma receptor [4] & to vitamins. Folate receptor (FR) is a well characterised, much studied and one of the most exploited receptors for drug delivery and imaging, as this GPI-anchored surface bound receptor is overtly expressed in multiple malignancies. Folic acid (FA), the vitamin B9, is the most potent FR-ligand. FA is exploited numerous times for imaging and delivery of bioactive molecules to cancers over-expressing FR. On using the same strategy of conjugating cationic lipid to folic acid, we obtained an entirely different observation. The conjugate allowed dual targeting and delivery of anticancer drug to both tumor-associated epithelial cells and macrophages (TAM) [5]. This angle of TAM delivery, we believe, opened up new formulation strategies for effective cancer treatment.

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GREEN SYNTHESIS OF STARCH MEDIATED GOLD NANOFLOWERS WITH IN VITRO ANTIMICROBIAL AND ANTICANCER ACTIVITIES

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Abstract:

Background: Starch has received great importance during last few years as a stabilizing agent for the synthesis of shape specific synthesis of Au NPs for biological application (Dauthal and Mukhopadhyay 2016). However, majority of the starch-mediated synthesis reported are either chemical based methods and/or produce Au NPs that are spherical or polyhedral in nature. But in contrast, application of starch as template for the synthesis of highly branched nanoparticles such as nanoflowers using plant extract as reducing agent has not been seen in literature.

Objectives: The present study shows shape selective green synthesis of Au NPs using aqueous seed extract of *Syzygium cumini* (L.) Skeels as reducing agent and starch as a template.

Methods: We describe an *in situ* method of synthesizing highly branched gold nanoflower (AuNFs) using aqueous seed extract of *Syzygium cumini* (L.) Skeels as reductant in the presence of 0.3% starch. Surprisingly, when the same reaction was carried out in the absence of starch or with starch at a lower concentration (0.15%), instead of flower-like morphology quasi-spherical or polyhedral nanoparticles (AuNPs) are obtained. The Au NPs were extensively characterized by HRTEM, FESEM, UV–Vis, FTIR, XRD, XPS and TGA analysis. The biological activities of the materials were investigated for antimicrobial activities against four bacterial strains that include one Gram positive (*Staphylococcus aureus* MTCC 121), two Gram negative (*Escherichia coli* MTCC 40 and *Pseudomonas aeruginosa* MTCC 4673) and one fungi (*Candida albicans* MTCC 227).

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Results & Discussions: The nanoparticles functioned as effective antimicrobial and anti-biofilm agents against all the strains under study. AuNFs showed improved efficacy as compared to conventional polyhedral shaped Au NPs against all the microbes under study which might be attributed to the larger surface-to-volume ratio of the nanoflowers. The AuNFs also showed effective in vitro anticancer activity against a human liver cancer cell line (Hep G2) with no significant cytotoxicity. Our data suggest that the AuNFs can significantly reduce the cancer cell growth with IC_{50} value of 20 $\mu g\ mL^{-1}$.

Conclusions: In conclusion, we described a morphology-controlled synthesis of Au NPs using aqueous seed extract of *Syzygium cumini* (L.) as bio-reductant. The Au NPs function as effective antimicrobial and anti-biofilm agents against four bacterial strains. Control experiments revealed that the flower-like nanoparticles are more effective than the polyhedral nanoparticles. The AuNFs also showed effective *in vitro* anticancer activity against liver cancer HepG2 cell line with no significant cytotoxicity.

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