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Keynote Presentations

The Design, Synthesis, and Evaluation of Selective Chaperone Modulators and their Utility to Treat Diseases

Brian Blagg*

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Abstract

The heat shock protein 90 (Hsp90) molecular chaperone is composed of four family members that play key roles in the folding of nascent polypeptides as well as the rematuration of misfolded proteins. The cytosolic chaperones, Hsp90a and Hsp90b, contribute to tumorigenesis and represent attractive targets for the treatment of cancer. Grp94 is the endoplasmic reticulum-localized paralog that is responsible for the trafficking of proteins, such as myocilin, and consequently represents an ideal target for the treatment of primary open-angle glaucoma. In contrast to the inhibition of Hsp90, molecular chaperones can be overexpressed to exhibit neuroprotective activity, which is currently undergoing phase II clinical evaluation. While the Hsp90 isoforms play key roles in various diseases, the N-terminal ATP-binding site is >85% identical, making the development of selective inhibitors challenging. In this presentation, the methods used to develop isoform-selective inhibitors will be disclosed, along with some of the preclinical studies that are currently underway.

Bending the Cost and Time Curve for Drug Discovery - From RNA Code to RNA Therapeutics in One Week

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Genomic Expression Inc, Beverly, Massachusetts, United States

Abstract

RNA is the software of life and by decoding RNA it is possible to record biology. Genomic expression has developed and clinically validated an RNA artificial intelligence (AI) enabled platform that in principle is disease agnostic. Approximately 50 - 80% of cancer patients do not benefit from their treatment, which costs an average of $2 billion to develop, with a mere 5% success rate. Cancer's heterogeneity is overlooked, with treatments still primarily based on tissue origin and limited biomarkers and a static one drug treatment paradigm. Current cancer therapies are mostly targeting cell surface proteins representing 250 of the 20,000 coding genes while the next generation of drugs can recode the cell biology from inside the cell. We proved our RNA AI platform can repurpose approved drugs on an individual patient basis with a 100% diagnostic yield and powerful anecdotal outcome data from late-stage cancer patients that is now in remission for years. We are now building translational capabilities that enable RNA-code to RNA therapeutics in weeks. Leveraging RNA AI, we can create innovative therapeutics, conduct combinatorial clinical trials tailored to individual patients, and monitor therapy responses in liquid biopsy samples. This shift from a static to a dynamic treatment paradigm enables timely adjustments to more effective therapies and quicker enrollment in clinical studies, enhancing patient outcomes. Today OneRNA® is saving lives helping cancer patients and their doctors navigate treatment options and pharma and biotech companies design and execute de-risked combinatorial studies identifying companion drugs and patients. Tomorrow we can bend the time and cost curve for new drug discovery and development.

Eliminating Implant Failure in Humans with Nano Chemistry: 30,000 Cases and Counting

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[2]*Division of Pre-College and Undergraduate Programs, Brown University, Providence, United States*

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Abstract

Nanomedicine is the use of nanomaterials to improve disease prevention, detection, and treatment which has resulted in hundreds of U.S. Food and Drug Administration approved medical products. While nanomedicine has been around for several decades, new technological advances are pushing its boundaries. For example, this presentation will present an over 25-year journey of commercializing nano orthopedic implants now in over 30,000 patients to date showing no signs of failure. Current orthopedic implants face a failure rate of 5 - 10% and sometimes as high as 60% for bone cancer patients. Further, artificial intelligence (AI) has revolutionized numerous industries to date. However, its use in nanomedicine has remained few and far between. One area where AI has significantly improved nanomedicine is through implantable sensors and neurological applications. This talk will present research in which implantable sensors, using AI, can learn from patient's response to implants and predict future outcomes. Such implantable sensors not only incorporate AI, but also communicate to a handheld device, and can reverse AI predicted adverse events. Examples will be given in which AI implantable sensors have been used in neurology to inhibit implant infection and promote prolonged neural function. Moreover, *in vitro* and *in vivo* experiments will be provided that demonstrate how nanotechnology can be incorporated into neurology to help human health.

Clinically Significant Drug-dietary Supplement Interactions Causing Treatment Failure or Drug Toxicity

Amitava Dasgupta*

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Abstract

Dietary supplements are sold in open market according to 1994 dietary supplement act without any U.S. Food and Drug Administration oversight. Approximately 50% U.S. population use such supplements. Many dietary supplements are used purely for general well-being and prevention of common ailments with a concept that such supplements are safe and effective. Although some supplements are safe and effective, others may cause harm. In the U.S. an estimated 23,000 emergency department visits annually are caused by significant toxicity related to use of dietary supplements. In addition, many dietary supplements also interact with drugs causing either treatment failure or drug toxicity. Approximately one fifth of Americans drink grapefruit juice in the morning with breakfast. Grapefruit juice increases bioavailability of many drugs most noticeably calcium channel blockers but also other drugs. Most common dietary supplements responsible for interactions with drugs include St. John's wort, kava, *Ginkgo biloba*, garlic, ginger and valerian. Active component of St. John's wort induces cytochrome P-450 enzyme causing reduced concentrations of many drugs including cyclosporine, tacrolimus, warfarin, protease inhibitors and others causing treatment failure. There are case reports of acute kidney rejection in stable patients after use of St. John's wort where trough tacrolimus concentrations were reduced by more than 50%. Moreover, St. John's wort may cause serotonin syndrome if used concurrently with selective serotonin reuptake inhibitor. Many dietary supplements including garlic and ginger potentiate pharmacological action of warfarin thus increasing risk of bleeding. In this talk treatment failure or drug toxicity due to interactions between dietary supplements and drug will be addressed including application of therapeutic drug monitoring in identifying certain clinically significant dietary supplement-drug interaction.

Novel Anti-inflammatory Tricyclic Compound Protects in Animal Models of Stroke, Alzheimer's, and Huntington's Diseases

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Abstract

Many neurological and psychiatric conditions entail and may be driven by inflammation. These observations led us to develop parallel high-throughput screens to discover small molecules which inhibit age-related Abeta proteotoxicity in a *Caenorhabditis elegans* model of Alzheimer's disease (AD) and microglial tumor necrosis factor-alpha (TNF-α). These studies led to the development of a novel small molecule, GM310, which inhibits the secretion of most pro-inflammatory cytokines from mouse microglia and TNF-α from human monocytes and is highly concentrated in brain after oral delivery with no apparent toxicity. GM310 produces molecular responses highly similar to those produced by dietary restriction and the ketogenic diet, including a gene profile indicating a shift away from glycolysis and toward metabolism of alternate (e.g., lipid) substrates, functionally corroborated by flux analysis. GM310 was protective in models of Alzheimer's, Huntington's, and hemorrhagic stroke, and increased lifespan. The glycolytic inhibitor 2-deoxy-D-glucose also inhibited microglial TNF-α and other markers of inflammation, delayed impairments in the *C. elegans* model of AD, and increased lifespan. Further studies indicated that the likely target of GM310 is the sigma-1 receptor, for which it apparently has a higher affinity than any known ligand. Pharmacoepidemiologic studies indicate that U.S. Food and Drug Administration-approved drugs structurally similar to GM310 reduce the risk of Alzheimer's Disease. Novel machine learning algorithms also predicted protective effects of GM310 and strongly implicated inhibition of C-terminal binding protein 2 as mediating protective effects of these protective effects. These results illustrate the value of combining phenotypic screens with machine learning for drug discovery as well, especially neurological and psychiatric diseases.

Radiation Sterilization Workflow Optimization Using Virtual Dose Mapping

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Abstract

Sterilization is a critical step in the manufacturing process of medical and pharmaceutical products but selecting the right modality and optimizing workflows can be challenging. This talk explores how virtual dose mapping enables manufacturers to evaluate radiation sterilization feasibility, identify the most suitable technology, and optimize packaging configurations. Virtual dose mapping can be delivered entirely as a service, implemented in-house using software, or through a hybrid approach-providing flexibility to meet diverse operational needs. By leveraging simulation, companies can reduce costs, accelerate validation, and improve process efficiency.

De-risking the Designer Milk Exosome Technology

Janos Zempleni*, Barbie Zaman Wahid, Xinyuan Zhang and Qamar Taban

University of Nebraska-Lincoln, Lincoln, United States

Abstract

We introduced designer milk exosomes (DMEs) as a vehicle for delivering gene therapy. DMEs delivered genes and gene editors with heretofore unknown specificity and potency to distinct tissues and cell types. In anticipation of questions to be asked by regulatory agencies and patients, we conducted a series of studies aimed at de-risking DME technology. First, we devised a protocol for increasing the homogeneity of DMEs. The protocol involves four steps: ultracentrifugation, size exclusion chromatography, sucrose density centrifugation, and affinity purification. Exosome marker proteins, CD9, and CD81, were

enriched ~12.5-fold in DMEs compared to input material (naïve MEs), whereas contaminants, β-lactoglobulin and histone H3, were not detectable. The scale of production is favorable. A single cow secretes more than 20,000 pounds of milk and 10 (exp21) naïve MEs annually. Using 11.4 L milk as starting material, we obtained 10 (exp)12 purified DMEs after completing the four purification steps. The yield is sufficient for treating patients and dosing large animals. Endotoxin levels were low in DME suspensions (<0.05 EU/mL) and avian flu virus was not detectable. When suspensions of naïve MEs were filtered through a 0.22 μm membrane filter and treated with high pressure processing, no microbial growth was detectable. MEs did not elicit an immune response or adverse effects on liver and kidney function, erythropoiesis in mice, rats, and human immune cells *ex vivo*. Loss of DMEs during storage and shipping was prevented if trehalose (79.3 mM final concentration) was added to suspensions. We generated first insights into ME pharmacokinetics and dosing in mice. Following the oral administration of fluorophore-labeled MEs, levels peaked in the intestinal mucosa at 3 h, urine and plasma at 6 h, urine at 12 h, and tissues (lung, kidneys, and spleen) at 12 h. Twenty-four hours after administration of the fluorophore-labeled MEs, the fluorescence signal had returned to baseline levels. The apparent oral bioavailability equaled approximately 50%. A single oral dose of DMEs was sufficient to achieve maximal expression of a protein implicated in the Prader-Willi syndrome, MAGEL2, in the hypothalamus of mice. Data from studies in mice were reproducible in large animals. For example, when DMEs were decorated with a neuron homing peptide, loaded with a reporter gene expression plasmid, and delivered to swine by syringe feeding, the reporter gene was expressed in the brain.

Acknowledgments: Supported by NIH SCGE, NIGMS, NIFA A1511, USDA (Hatch and W-5002), Cure SYNGAP1, and Foundation for Prader-Willi Research. Janos Zempleni is a co-founder and co-owner and serves as Chief Science Officer of Mino Vacca, Inc.

Human Genetic Data to Advance Drug Repurposing and Discovery in Heart Failure

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Abstract

Heart failure is a complex, multifactorial syndrome with rapidly increasing prevalence and persistently high morbidity and mortality despite therapeutic advances. A key barrier to improved outcomes is the high attrition of drug targets that emerge solely from preclinical models, when tested in clinical trials. In contrast, multi-omic profiling—spanning genomics, proteomics, transcriptomics, metabolomics, and epigenomics—offers a powerful, human-centered route to therapeutic discovery and development. Notably, targets supported by human genetic evidence are substantially more likely to succeed in clinical trials and reach the market. When linked to robust electronic health record infrastructures, human-omics enable deep phenotyping at scale and accelerate novel genetic discovery. This lecture will highlight how human genomic data from the Million Veteran Program, one of the largest biobanks linked to a national electronic health record system, and systems biology approaches, can improve prioritization of actionable drug targets and inform prevention and treatment strategies for the growing heart failure epidemic.

Principles and Standards for Designing and Managing Integrable and Interoperable Transformed Health Ecosystems

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Abstract

Health and social care systems around the world undergo a transformation towards personalized, preventive, predictive, participative precision medicine (5 PM), considering the individual health status, conditions, genetic and genomic dispositions in personal, social, occupational, environmental and behavioral context. For enabling communication and cooperation between actors from different domains using different methodologies, languages and ontologies based on different education, experiences, etc., we must advance design and management of the resulting complex and highly dynamic ecosystem from data to knowledge level. The transformation is strongly supported by technologies such as micro- and nanotechnologies, advanced computing, artificial intelligence, edge computing, etc. Besides their opportunities, those advanced technologies also bear risks to be managed. Beside the relationships between technology and human actors, the behavior of intelligent and autonomous systems must be considered from a humanistic, moral and ethical perspective. The challenge is the consistent, correct and formal representation of the transformed health ecosystem from the perspectives of all domains involved including the legal and ethical

ones, representing and managing them based on related ontologies. The resulting business view of the real-world ecosystem must be interrelated using the International Organization for Standardization (ISO) and the International Electrotechnical Commission 21838 top level ontologies standard. Thereafter, the outcome can be transformed into implementable solutions. The different viewpoints are represented using viewpoint-specific information and communication technology ontologies. The necessary model and framework have been developed by the author and meanwhile standardized as ISO 23903 Interoperability and Integration Reference Architecture. The formal representation of any ecosystem and its development process including examples of practical deployment of the approach are presented in detail. This includes correct systems and standards integration and interoperability solutions.

Expanding the Repertoire of Methanocarba Nucleosides from Purine Receptors to Diverse Receptors and Transporters

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Abstract

Nucleoside derivatives are well represented as pharmaceuticals due to their druglike physicochemical properties, and we have designed nucleoside drugs to act on adenosine receptors. Moreover, we have characterized previously undetected interactions at diverse and unconventional targets and enhanced those activities by careful structure-activity relationship study. A general modification, i.e., a constrained, bicyclic ring system (bicyclo [3.1.0] hexane, also called methanocarba) substituted in place of a furanose ring, can increase nucleotide potency and/or selectivity at purinergic and nonpurinergic targets. Compared to other common drug discovery scaffolds containing planar rings, methanocarba nucleosides display greater sp3 character (i.e., more favorable as drug-like molecules) and can manifest as sterically constrained North (N) or South conformations. Initially weak, off-target interactions of (N)-methanocarba adenosine derivatives were detected as leads that were structurally optimized to enhance activity and selectivity toward target proteins that normally do not recognize nucleosides. By this approach, novel modulators for 5HT2B serotonin and opioid receptors, dopamine (DAT) and ATP-binding cassette transporters were found, and other activities were revealed and optimized. The allosteric inhibitor MRS7292 enabled the first cryo-electron microscopy determination of the structure of human DAT. Thus, through methanocarba nucleoside synthesis, multi-target pharmacology, and structure-activity relationships, a robust purinergic receptor scaffold has been repurposed to satisfy the pharmacophoric requirements of various G protein-coupled receptors and transporters.

Featured Presentations

Artificial Intelligence/Machine Learning in Packaging Innovations for Drug Discovery

Anupam Chanda*

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Abstract

Artificial intelligence/machine learning (AI/ML) plays a most significant role in packaging development, packaging machines in R&D and commercial production. Not only in online "liquid injection inspection" areas but in semi solids, gel, labels for vials, pre-filled syringes, plastic bottle, flexible pouches and many pharmaceutical doses form. Python is widely used in AI due to its simplicity and versatility. Rich selection of libraries for ML and data analysis. It allows developers to create intelligent systems that can learn from data, recognize patterns, and make decisions.

Kera's Software: Facilitates tasks like image classification, object detection and video analysis through easy-to-implement convolutional neural networks (CNNs). And ideal for applications from medical imaging diagnostics to automated manufacturing quality control.

Open CV Software: Possibilities in computer vision applications and enhanced object detection to sophisticated image recognition.

Tensor Flow Software: Natural language processing; Computer vision; Object detection; Exact recognition; and Building CNNs.

AI ensures precision in tablets, capsules, label text matters, barcodes. Vial and pre-filled syringe inspection. Maintaining rigorous quality control standards when mass-producing vials of liquid medicine can be challenging. Vials can be subject to contamination or cross-contamination can occur during manufacturing. These "defects" cannot be tolerated. Detecting these issues is nearly impossible for the human eye, especially when vials are produced at a high rate. AI-powered machine vision solutions. AI software helps pharmaceutical companies detect contaminants, identify defects, ensure consistent fill levels, minimize consumer risk, and enhance overall product quality.

Use of Designer Milk Exosomes for Delivering Gene Therapy

Janos Zempleni*, Barbie Zaman Wahid, Xinyuan Zhang and Qamar Taban

University of Nebraska-Lincoln, Lincoln, United States

Abstract

Naïve bovine milk exosomes (MEs) possess qualities conducive to delivering therapeutic payload to pathological tissues. Qualities include production at scale, biological safety, oral bioavailability, large loading capacity (~12 kB), and the ability to cross barriers like the placenta and blood-brain barrier. MEs have in common with adeno-associated viruses and lipid nanoparticles limitations such as imperfect homing to target tissues and rapid elimination by host macrophages. We developed designer MEs (DMEs) which overcome these limitations while retaining all the positive qualities of naïve MEs. Briefly, naïve MEs are purified from milk by the sequential use of size exclusion chromatography, sucrose density gradient centrifugation, and affinity chromatography to achieve maximal homogeneity. MEs are functionalized by attaching synthetic homing and don't-eat me peptides using hydrazide chemistry. We reported that the hydrazone bond formed is stable in stomach, intestine, and plasma. We steered DMEs to seven distinct tissues, regions of the brain, and cell types, which was paralleled by a substantial decrease of DME levels in off-target tissues in swine and mice. Decoration of DMEs with a don't-eat-me peptide, CD47, decreased internalization by murine bone marrow-derived macrophages by 50%, leading to a 12-fold increase in plasma levels and complete penetration of the brain in mice. Reporter plasmid payload, delivered orally or by minimally invasive nasal spray, was expressed in the porcine and murine brain. Plasmids restored gene expression to wild-type levels in a mouse model of an ultrarare disease, SYNGAP1 haploinsufficiency, and were expressed in a model of a rare disease, Prader-Willi syndrome. DMEs, decorated with homing peptides to hippocampus, heart, or pancreas and loaded with clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated protein 9, targeting enhanced green fluorescent protein (EGFP) eclipsed EGFP fluorescence in respective target tissues, while not altering fluorescence in kidneys, liver, and spleen in reporter mice. We conclude that DMEs are a promising vessel for delivering gene therapy to hard-to-reach pathological tissues.

Acknowledgments: Supported by NIH SCGE, NIGMS, NIFA A1511, USDA (Hatch and W-5002), SYNGAP Research Fund, and Foundation for Prader-Willi Research. Janos Zempleni is a co-founder and co-owner of Minovacca, Inc.

VGP28 - A Postbiotic Metabolite of Natural Origin as a Novel Drug Lead in Atopic Dermatitis

Jakub P. Piwowarski*, Joanna Giebultowicz, Joanna Kolmas, Sebastian Granica and Maciej Dawidowski

Medical University of Warsaw, Poland

Abstract

Traditionally used plant materials can be bio transformed by the human gut microbiota into postbiotic metabolites whose structures and biological activities differ markedly from those of the original compounds. This perspective offers new insights into the mechanisms behind the pharmacological effects of medicinal plants and underscores the substantial potential for identifying novel bioactive molecules formed through microbial metabolism of plant specialized metabolites. Such strategies pave the way for discovering new lead compounds suitable for further pharmaceutical development. VGP28 is a postbiotic metabolite generated from tannins by human gut microorganisms, characterized by a strong ability to suppress macrophage-mediated inflammatory responses. Its high anti-inflammatory potency, combined with limitations related to rapid deactivation following oral administration, provides a strong rationale for producing VGP28 in isolated form via chemical synthesis and applying it directly to sites of inflammation. The conducted research enabled the development of a scalable synthetic route to VGP28 and confirmed its anti-inflammatory activity *in vitro* in keratinocytes and fibroblasts, supporting its potential use in the topical treatment of inflammatory skin disorders of diverse origins. Additionally, a stable topical formulation of VGP28 was developed and evaluated in studies using human skin explants, further validating its suitability for dermatological applications.

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Upstream Process Intensification Using Perfusion Technology to Enhance Chinese Hamster Ovary - Based Production of Rare Disease Biologics

Ishwarya Pitta Karthikeyan*, Xinbo Zhang, Yajing Zhao, Justin Valles, Matt Wilhelm, Xiaolu Chen, Andrei Arion, Rob Ballinger, Andrew Yongky, Patricia Bento, Jack Huang and Siguang Sui

Alexion AstraZeneca Rare Disease, New Haven, United States

Abstract

Perfusion-based upstream intensification provides clear advantages over conventional fed-batch (FB) operations, delivering higher peak viable cell density (VCD), greater volumetric productivity (g/L/day), improved product quality through reduced residence time, and lower oxidative stress. We systematically assessed these approaches in Chinese hamster ovary cells producing four platform molecules under perfusion, testing cell performance and production yield against FB. These molecules are positioned to treat rare disease profiles like myositis, IgA nephropathy, lupus nephritis and hypophosphatasia (HPP). Implementing an N-1 perfusion stage consistently achieved VCDs >40 × 10^6 cells/mL, enabling 10 - 20-fold higher seeding densities into N-stage production bioreactors. Production reactors reached peak VCDs of >100 × 10^6 cells/mL and delivered ~4.68-fold gains in cumulative permeate productivity and ~6-fold increases in integral VCD (IVCD). For several molecules, product quality improved, with marked reductions in trisulfide formation and fragmentation. We currently employ tangential flow filtration techniques for our perfusion setup where two hollow-fiber modules (Repligen and Microza) were compared. Out of the two, Microza fibers yielded higher cumulative productivity under the tested conditions. As part of process analytical technology advancement, we have recently introduced in-line monitoring of glucose and VCD via Endress Hauser Raman spectrometer and Hamilton bio capacitance probe respectively. Our study also outlines mechanisms for platform optimization, including bioreactor configuration, feed optimization, filter fouling mitigation, oxygen transfer and shear management which leads to the development of more robust and intensified process development strategies.

Packing Challenges for Affordable Biosimilar Products

Anupam Chanda*

Bio2XyTran Inc., Boston, United States

Abstract

Presently packaging plays, a significant role for biosimilar products. The process of selecting materials and the type of packaging also offers an opportunity for the packaging scientist to look for new biological delivery choices. Most injectable protein products were supplied in some sort of glass vial, prefilled syringe, cartridge. Those products having high pH content there is a chance of "delamination" from inner surface of glass vial. With protein-based drugs, the biggest issue is the effect of packaging derivatives on the protein's three-dimensional and surface structure. These are any effects that relate to denaturation or aggregation of the protein due to oxidation or interactions from contaminants or impurities in the preparation. The potential for these effects needs to be carefully considered in choosing the container and the container closure system to avoid putting patients in jeopardy.

Cause of Delamination

- Formulations with a high pH include phosphate and citrate buffers increase the risk of glass delamination.
- High alkali content in glass could accelerate erosion.
- High temperature during the vial-forming process increases the risk of glass delamination.
- Terminal sterilization (irradiated at 20 - 40 kGy for 150 min) also is a risk factor for specific products (veterinary parenteral administration), could cause delamination.
- High product storage temperatures and long exposure times can increase the rate and severity of glass delamination.

How to Prevent Delamination

- Treating the surface of the glass vials with materials, such as ammonium sulfate or siliconization can reduce the rate of glass erosion.
- Consider alternative sterilization methods only in rare cases.
- The correct specification for the glass to ensure its suitability for the pH of the product.
- Use cyclic olefin copolymer/cyclic olefin polymer vial.

Adsorption of Protein and Solutions

- Option#1: Coat with linear methoxylated polyglycerol and hyperbranched methoxylated polyglycerol.
- Option#2: The hyperbranched non-methoxylated coating performed best.
- Option#3: Coat with hyperbranched polyglycerol.
- Option#4: Right selection of sterilization of glass vial/syringe.

Present market demand is syringe barrel and/or plunger coated with silicone. Non-uniform silicone coatings can affect protein stability. The proteins can absorb into the walls of the container. While silicone can reduce absorption, excess silicone can form suspended oil-like droplets. Proteins can form around those droplets and change their natural state. New lubricant coatings, such as inert fluoropolymers, are being introduced to replace silicone. As a very inert material, fluoropolymer provides smoothness for the syringe plunger without the irregularities or the issues that have come with silicone. Other new coating materials are being introduced with new types of packaging related to self-injectors, especially injector pens, patches, and transdermal and wearable devices for self-infusion (Figure 1). Extractable and leachable are most important for inhalers and catheters. For an extractable from a device component the analytical evaluation threshold (AET) (μg/g) can be determined using equation 1.

$$AET = SCT \times Dt/Dd \times m \quad (1)$$

Where, Dd is doses per day, Dt is totally labelled doses, and m is the mass of component.

The AET (μg/device) for a drug delivery device (e.g., a metered dose inhaler) can be determined from equation 2:

$$AET = SCT \times Dt/Dd \quad (2)$$



Figure 1: Biosimilar products.

Fighting Cancer Using Nanotechnology: An Over 25 Year Journey to Success

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[3]*School of Engineering, Saveetha University, Chennai, India*

Abstract

This presentation will cover a close to 25-year journey researching and commercializing nanotechnology for improving cancer prevention, diagnosis, and treatment which has led to numerous products including implants now in over 30,000 patients to date showing no return of cancer or signs of failure according to the U.S. Food and Drug Administration manufacturer and user facility device experience database. Traditional orthopedic implants face a failure rate of 5 - 10% and sometimes as high as 60% for bone cancer patients. The talk will cover not only human clinical evidence of the unprecedented efficacy of nanotechnology in medicine but also fundamental evidence of how nanotechnology can be used clinically to kill cancer cells, bacteria, inhibit inflammation, and promote tissue growth (if needed) without drugs. This talk will also describe the future of nanotechnology and how it will in the not too distant future combat traditional failures in our global healthcare system including reversing the current decrease in global average life expectancy, creating a reactive compared to predictive healthcare system, transforming a healthcare system that relies too much on drugs and pharmaceutical agents to treat ailments, facilitating a non-personalized healthcare system, combating increasing costs, treating a growing global population, and more through the future use of implantable nano sensors, 4-dimensional printed nano materials, smart nano materials, environmentally-friendly nanomaterials, and artificial intelligence as well as other predictive models in medicine and more.

The Structure of a Novel Rufomycin Click-chemistry Analog Bound to MtbClpC1-NTD Reveals a Unique Dimeric Complex: Description and Implications

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Abstract

Disrupting protein homeostasis in *Mycobacterium tuberculosis* has emerged as a novel strategy for developing potent anti-tuberculosis agents. Natural products such as cyclomarin A, rufomycin 4/6 (RUF), and ecumicin target the ClpC1P1P2 protein degradation complex in *M. tuberculosis*, making it a promising therapeutic target. This study employed click chemistry to generate conformationally constrained analogs of RUF, producing both monomeric (intramolecular click reaction) and dimeric (intermolecular click reaction) derivatives. Comprehensive biophysical and biochemical analyses, combined with X-ray crystallography and computational modeling, showed that dimer 'intermolecular' analogs containing two longer tethers maintained the active conformation, and enabled strong binding to ClpC1NTD with prolonged residency time, resulting in significantly enhanced ClpC1 ATPase activity. These findings highlight the potential of dimeric click chemistry analogs as innovative anti-tuberculosis agents and molecular tools for studying bacterial protein degradation.

Lipid Nanoparticle Delivery of Transposase-based Gene Editing to Treat Retinal Disease

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Abstract

Genome editing–based gene therapies using non-viral delivery systems are well regarded for their permanence and precision. Several types of genome editing tools are available that can make small corrections; however, technologies capable of inserting large genes are rare. Many genetic diseases are caused by a single gene, but within that gene, multiple different mutations may contribute to disease. Using clustered regularly interspaced short palindromic repeats-based small editing tools to correct these mutations would require multiple edits (products) to fix all the faults within that gene. Therefore, a genome editing tool capable of restoring an entire faulty gene's function is desirable. Transposases are one such class of tools. Key challenges with this technology are the delivery of two nucleic acids - DNA and RNA, minimizing off-target biodistribution, safety, and ensuring a high cellular uptake/expression. A variety of non-viral delivery systems were investigated, and lipid nanoparticle (LNP) system was selected. The LNP formulation composition and manufacturing were optimized via evaluating *in-vitro* expression, *in-vivo* tolerability, and protein expression. In-depth characterization of the LNP was performed to assure product consistency, safety and efficacy. Abca4/mice treated with optimized LNP, encapsulating transposase mRNA and hABCA4 DNA, showed great tolerability and significant ABCA4 protein expression in the photoreceptors that should translate into a significant therapeutic benefit to the patient.

Investigation of Novel Pyrazolo[4,3-e]Tetrazolo[1,5-b] [1,2,4]Triazine Sulfonamide Derivatives as Potential Candidates Against Colon Cancer

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Abstract

Background and Aims: Cancer therapy is one of the most important challenges of modern medical and chemical sciences. Among the many methods of combating cancer, chemotherapy plays a special role. Imperfect modern chemotherapy justifies continuing the search for new, more effective, and safe drugs i.e. without an impact on normal cells. Recent literature reports show that sulfonamide derivatives have antitumor activity *in vitro* and *in vivo*. Thus, the objective of this study was to synthesize novel pyrazolo[4,3-e]tetrazolo[1,5-b][1,2,4]triazine sulfonamide derivatives with anticancer potential against colon cancer cells.

Results: The research carried out included methyl thiazolyl tetrazolium assay, DNA biosynthesis, cell cycle analysis, annexin V binding assay, ethidium bromide/acridine orange staining, and caspase-8, -9, and -3/7 activity. Moreover, the concentrations of important molecules (soluble intercellular adhesion molecule-1 (sICAM-1), mechanistic target of rapamycin (mTOR), Beclin-1, cathepsin B) involved in the pathogenesis and poor prognosis of colorectal cancer were also evaluated by enzyme-linked immunosorbent assay. Obtained results demonstrated that the novel compounds were able to induce apoptosis through intrinsic and extrinsic pathways and was capable of decreasing sICAM-1, mTOR, cathepsin B concentrations, whereas increased Beclin-1 concentration was detected in both colon cancer cell lines (digital lymphnode derived – 1 (DLD-1) and human tumor – 29 (HT-29).

Conclusions: The novel compounds represent promising multi-targeted potential in colorectal cancer. They inhibit the viability and proliferation of DLD-1 and HT-29 cells. The molecular mechanism of action is associated with the induction of both extrinsic and intrinsic apoptotic pathways. This is related to increased Caspase-8 and Caspase-9 activity. The derivatives can inhibit important proteins engaged in the progression and metastasis of colorectal cancer such as sICAM-1, cathepsin B, and mTOR.

Integrative Bioinformatics and Experimental Insights into Melanoma Pathology

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Abstract

Melanoma progression and therapeutic resistance arise from complex biological programs that are incompletely captured by single-omic analyses. This lecture highlights how integrative bioinformatics, combined with experimental and clinicopathologic validation, has advanced understanding of melanoma pathology, with emphasis on my work on undifferentiated/dedifferentiated melanoma and melanoma brain metastases (MBMs). Undifferentiated melanomas lack conventional melanocytic morphology and immunophenotype, creating diagnostic challenges. Integrated genomic analyses demonstrate that these tumors nonetheless retain defining molecular features, including enrichment for neuroblastoma Ras viral oncogene homolog and Ras-related C3 botulinum toxin substrate 1 alterations and strong ultraviolet mutational signatures, underscoring the importance of molecular context in classification. In MBMs, multi-omic profiling of patient- matched brain and extracranial metastases reveals profound immune suppression within the brain microenvironment despite largely shared mutational landscapes. Transcriptomic analyses show decreased immune infiltration and signaling in MBMs, correlating with inferior clinical outcomes. Metabolic reprogramming emerges as a key determinant of brain metastatic fitness. Oxidative phosphorylation (OXPHOS) is consistently enriched in MBMs and is functionally required for intracranial tumor growth, including in mitogen-activated protein kinase inhibitor-resistant disease. Genetic inhibition of the PGC1α/OXPHOS axis significantly reduces lung and brain metastasis formation *in vivo*. Mechanistically, loss of the epigenetic regulator ten-eleven translocation 2 promotes expression of PGC1α/OXPHOS through altered enhancer hydroxy methylation, linking epigenetic dysregulation to metabolic adaptation. Together, these studies illustrate how integrative, multi-omic strategies reveal biologically and clinically actionable insights into melanoma progression that are not apparent from genomic data alone, providing a framework for therapeutic targeting of aggressive and treatment- refractory melanoma.

Conjugated Lipid Nanoparticles for *In-vivo* CAR-T Therapy: Scientific Foundations and Translational Chemistry, Manufacturing, and Controls Challenges

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Abstract

In vivo chimeric antigen receptor T-cell (CAR-T) therapy is rapidly emerging as a transformative approach in cancer treatment, offering a more direct, scalable alternative to today's complex and costly *ex vivo* processes. At the center of this shift are conjugated lipid nanoparticles (CLNPs) engineered non-viral carriers that deliver mRNA encoding CAR transgenes directly to T cells in the body. By coupling LNPs with targeting ligands such as antibodies, peptides, or small molecules, developers aim to achieve cell-specific delivery with very high precision. However, translating this technology from research to clinical application introduces a new layer of chemistry, manufacturing, and controls (CMC) complexity. Ensuring particle stability post- conjugation, maintaining consistency during scale-up, developing meaningful potency assays, and meeting evolving regulatory expectations all present significant hurdles. This review explores the scientific principles behind CLNP-based *in vivo* CAR-T therapy, the key CMC challenges impeding its development, and emerging strategies that could enable this promising technology to move from concept to clinical reality.

Role of Artificial Intelligence/Machine Learning and Data Science in Pharmaceutical Company

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Abstract

Artificial intelligence (AI) has emerged as a powerful tool that harnesses anthropomorphic knowledge and provides expedited solutions to complex challenges. Remarkable advancements in AI technology and machine learning (ML) present a transformative opportunity in the drug discovery, formulation, and testing of pharmaceutical dosage forms. By utilizing AI algorithms that analyze extensive biological data, including genomics and proteomics, researchers can identify disease-associated

targets and predict their interactions with potential drug candidates. This enables a more efficient and targeted approach to drug discovery, thereby increasing the likelihood of successful drug approvals. Furthermore, AI can contribute to reducing development costs by optimizing research and development processes. ML algorithms assist in experimental design and can predict the pharmacokinetics and toxicity of drug candidates. This capability enables the prioritization and optimization of lead compounds, reducing the need for extensive and costly animal testing. Personalized medicine approaches can be facilitated through AI algorithms that analyze real-world patient data, leading to more effective treatment outcomes and improved patient adherence. This comprehensive review explores the wide-ranging applications of AI in drug discovery, drug delivery dosage form designs, process optimization, testing, and pharmacokinetics/pharmacodynamics studies. This review provides an overview of various AI-based approaches utilized in pharmaceutical technology, highlighting their benefits and drawbacks. Nevertheless, the continued investment in and exploration of AI in the pharmaceutical industry offers exciting prospects for enhancing drug development processes and patient care.

Artificial Intelligence (AI) and Alternative Variables in Drug Discovery: A Promising Alliance

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Abstract

The power of artificial intelligence/machine learning (AI/ML) methods and algorithms lies in the extension and generalization of certain established mathematical concepts into a more comprehensive framework allowing the manipulation of new variables to extract patterns in experimental data. In the context of drug discovery, inclusion of already available alternative variables (e.g., ligand efficiencies), and the visual concepts derived from them (e.g., efficiency planes), could provide a unique synergy that could benefit both the AI/ML and drug discovery communities, to advance their societal goals.

Applications of Artificial Intelligence/Machine Learning and Data Science Pharma Business Growth

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Abstract

Business intelligence (BI) in pharma encompasses the tools and insights that help companies make data-driven decisions across research, drug development, manufacturing and commercial operations. Today's pharmaceutical firms handle massive data sets from experimental results and clinical trial records to supply chain logs and real-world patient outcomes. Artificial intelligence (AI) has emerged as a critical enabler to extract actionable intelligence from this deluge of data, promising faster drug development, smarter trials, efficient production, and sharper market strategies. In fact, global AI in pharmaceutical market is estimated at $1.94 billion in 2025 and is forecasted to reach around $16.49 billion by 2034, accelerating at a compound annual growth rate of 27%. McKinsey estimates that generative AI alone could generate $60 billion to $110 billion a year in economic value for the pharma and medical-product industries. This comprehensive report surveys the landscape of AI-powered BI software for pharma, covering both commercial and open-source tools. We categorize solutions by their primary use case – from early drug discovery and clinical trial optimization to supply chain, real-world evidence analytics, market intelligence and regulatory compliance. For each category, we highlight key platforms, their capabilities and underlying AI technologies (Machine Learning), natural language processing, computer vision, generative models, etc.), examples of pharma use and recent trends.

Advancing Carvacrol as a Phytopharmaceutical Candidate: Preclinical Validation and Translational Development Strategy

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Abstract

The transformation of bioactive natural compounds into clinically relevant therapeutic candidates requires systematic pharmacological validation and strategic positioning within the pharmaceutical R&D pipeline. Carvacrol, a monoterpenoid phenol widely recognized for its anti-inflammatory, antioxidant, antimicrobial, and tissue-modulatory properties, has emerged as a promising lead phytochemical with multitarget activity. This presentation will summarize our integrated preclinical investigations exploring the biological and mechanistic profile of carvacrol-based formulations. Emphasis will be placed on functional validation in experimental models, modulation of extracellular matrix dynamics, regulation of pro-angiogenic and growth factor signaling pathways, and inhibition of matrix-degrading enzymes. These coordinated effects highlight carvacrol's capacity to influence key molecular processes involved in inflammation resolution and regenerative progression. Beyond pharmacodynamic evaluation, critical pharmaceutical development aspects will be addressed, including formulation strategy, active marker standardization, route-of-administration optimization, and translational positioning toward scalable therapeutic applications. Collectively, the available preclinical evidence supports the advancement of carvacrol as a mechanism-driven phytopharmaceutical candidate. This work illustrates how rational phytochemical development, supported by molecular validation and formulation design, can contribute to innovative therapeutic strategies within contemporary pharmaceutical research and development framework.

Benzimidazole Anti-nematode Drugs in Veterinary Medicine – Are They Likely to Interfere with Non-target Invertebrates?

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Abstract

Benzimidazoles are amongst the most important contemporary anti-nematode drugs. They target nematodes by binding to parasite β-tubulin and inhibiting microtubule polymerization, which results in the destruction of cell structure and subsequent death of the parasite. Benzimidazoles' affinity for nematode tubulins is higher than that for mammalian tubulins, which makes them relatively safe for mammals undergoing treatment (horses, pigs, sheep, and cattle). Studies on benzimidazoles' activity towards non-target invertebrates, e.g. earthworms are scarce - in 2025. Gao reported reproductive toxicity of albendazole for *Eisenia fetida*. Selected drugs used to control nematode invasions in animals were evaluated in the context of their potential toxicity for earthworms. Novel classification and regression models were developed using experimental toxicity data. The mobility of studied compounds in the soil-water compartment was assessed using a novel predictive model. The interactions of studied benzimidazoles with enzymes: glutathione S-transferase (PDB:1M0U); superoxide dismutase (PDB:1CBJ); catalase (PDB:1TGU); guaiacol peroxidase (PDB:1GZA) were studied by molecular docking. It was established that all drugs from the studied group are moderately mobile in soil, so they can spread relatively far from a point of discharge (e.g. when they reach the soil with natural fertilizers). The affinity of studied benzimidazoles for key enzymes presents in earthworms and responsible mainly for earthworms' protection against harmful xenobiotics is relatively high. The consequences of benzimidazole anti-nematode drugs' presence in soil may include disruption of earthworms' protective mechanisms against harmful xenobiotics, reproductive issues and increased mortality, but the exact degree of risks should be established by further studies.

Validated Protocol Based on Micro-solid-phase Extraction Sample Preparation and High-performance Liquid Chromatography Coupled with Triple Quadrupole Tandem Mass Spectrometry Analysis for Therapeutic Monitoring of Janus Kinase Inhibitor Drugs Indicated for the Treatment of Inflammatory Bowel Disease in Clinical Serum Matrices

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Abstract

Inflammatory bowel disease (IBD), mainly affecting people of working age, is a group of chronic, immune-mediated disorders characterized by long-term inflammation of the digestive tract (primarily consisting of Crohn's disease and ulcerative colitis), with increasing incidence. Janus kinase inhibitors (JAKis) represent one of the newest modalities for the treatment of IBD. In this context, therapeutic drug monitoring of JAKis remains an evolving field, primarily due to the absence of validated therapeutic targets and heterogeneous pharmacokinetic profiles of individual agents. To study the relevance of systemic exposure from various perspectives, reliable quantification of JAKis is essential. In the present work, therefore, a complex validated protocol for the quantification of clinically relevant serum concentrations of JAKis, based on a micro-solid-phase extraction (μSPE) sample preparation and high-performance liquid chromatography coupled with electrospray ionization and triple quadrupole mass spectrometry analysis, was developed. The optimized workflow, systematically validated following U.S. Food and Drug Administration guidelines for biomedical methods, provides several important benefits. The first is a uniform sample preparation and analysis procedure enabling simultaneous determination of the JAKis currently approved for IBD therapy (by European Medicines Agency/U.S. Food and Drug Administration). The second, greening of both sample preparation and chromatographic analysis through appropriate solvent selection. The third, a simple and high throughput μSPE sample preparation step for the subsequent analysis of total concentration levels of JAKis. The fourth, a robust and highly reliable performance for therapeutically relevant JAKis concentration levels. The applicability of the elaborated protocol was demonstrated in a pilot real-world exposure monitoring study including serum samples from IBD patients treated with tofacitinib, upadacitinib, and filgotinib, respectively. Serial opportunistic sampling enabled characterization of exposure variability and detection of treatment interruption or non-adherence. Concentration-matched verification (comparing concentration-matched serum standards with the corresponding clinical samples), further confirming reliable quantification in authentic biological matrices, accomplished the demonstration of the method suitability for its routine clinical use.

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Treatment of Choroidal Melanoma by Leksell Gamma Knife - 25 years of Experience

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Abstract

Retrospective non-randomized trial investigated the effect of gamma irradiation on malignant choroidal melanoma in the eye by using Leksell Gamma Knife Surgery (LGKS). We started to use stereotactic irradiation on choroidal melanoma in year 2000 ordinarily. Survival in horizon of 5 year was recorded in over 70% of all stages of tumors, treated by LGKS. Results were reported for 800 patients compared to the pre-treatment status investigated, eyes showed significant reduction of tumor volume and blockage of spreading tumors. We also objectified saving of visual function of no affected parts of the Eye. After LGKS we could also perform further surgery with no risk of general metastasis of tumor.

Characterization and Functional Activity of Hybrid Silica Matrices and Nanogels More Magic Molecules: Nitroxide Nanoparticles and their Applications

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Abstract

Nitroxides are a class of relatively stable free radicals that were initially employed in electron paramagnetic spectroscopy and later gathered much interest in their antioxidant activity and are currently studied for a range of applications. Many of these applications can benefit from encapsulation of nitroxides within nanoparticles. We have experience in silica-based sol-gel matrices and encapsulation of biomolecules of interest within. These sol-gel derived solid matrices are made of a -Si-O-Si-O- amorphous network and exhibit a range of advantageous properties including being structurally stable, optically transparent, chemically inert and extensively porous with a large surface area to mass ratio. Such matrices are utilized for encapsulation of proteins where under specific gelation conditions the encapsulated proteins remain structurally intact and functional. Thus, the sol-gel matrix can serve as a platform to study the structure function relationship of the entrapped proteins. It also serves unique properties for utilizing proteins such as the catalytic activity of enzymes in a variety of applications. The extension of this approach to the formation of sol-gel based nanoparticles (nanogels) combines the advantageous sol-gel encapsulation matrix environment with the inherent advantages of nanoparticles. Here we report on our progress in fabrication of silica-based sol-gel hybrid nanogels with entrapped nitroxide species and present the result of the characterization of these hybrid nanogels and the nitroxides within.

A Review on Aortic Cholesterol Efflux Using Interleukins that Upregulate ATP-binding Cassette Transporter ABCA1 and ABCG1 in Atherosclerosis Study Models

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Abstract

Atherosclerosis is the result of lipid accumulation in the vascular wall within endothelial cells (EC) and underlying intimal cells. Atherosclerotic accumulation in arteries is often found within EC and underlying intimal cells. Lipid-laden vascular smooth muscle cells and macrophage cells are molded into macrophage like foam cells to initiate inflammation in atherosclerosis. We previously reported that interleukin (IL)-27 was found in decreased state in the abdominal aortic aneurysm disease model. Others report that IL-27 enhanced aortic cholesterol efflux and upregulated ATP-binding cassette transporter ABCA1 and ABCG1 expressions. Here we reviewed aortic cholesterol efflux using IL-27 aortic neovascularization in aneurysm and atherosclerosis disease state. We performed the standard collection of published reports and performed through review of those data with standard methods including meta-analysis or whichever was appropriate. The data involved peer-reviewed articles involving *in vitro*, *in vivo* and review studies. The tables, images, and concepts were analyzed with critical review. Our findings demonstrate that the therapeutical targeting of aortic cholesterol efflux using protein molecules provides significant information for the therapeutical study of vascular damage repair in cardiovascular diseases.

Development of Novel Drug Delivery Pathways Enabled by Perillyl Alcohol (NEO100), A Monoterpene with Multifaceted Biomedical Applications

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Abstract

Perillyl alcohol is a naturally occurring monoterpene related to limonene. We have synthesized a clinical-grade version, called NEO100 (NeOnc Technologies, Inc., Los Angeles, California, USA), which has revealed a variety of highly promising characteristics that we are exploring toward the development of improved cancer-therapeutic regimens. (i) NEO100 can be

delivered via intranasal applications, which exploits direct nose-to-brain transport, and an ongoing phase 2a clinical trial with recurrent malignant glioma patients is generating intriguingly positive results. (ii) In preclinical brain cancer models, we have shown that intranasal NEO100 can act as a carrier to enable nose-to-brain delivery of other cancer drugs directly to the malignant lesions in the brain. (iii) When given via intra-arterial injection, NEO100 was shown to safely and reversibly open the blood-brain barrier (BBB) of mice, which enabled other cancer drugs circulating in the bloodstream to effectively enter the brain and kill brain cancer cells; in the absence of NEO100, these drugs were unable to cross the BBB and did not exert brain-targeted activity. (iv) In further applications, we covalently conjugated NEO100 to other, already established drugs. For example, conjugation of NEO100 to temozolomide, an alkylating agent, resulted in a novel fusion compound called NEO212 (NeOnc Technologies). Our studies in diverse preclinical tumor models established that NEO212 is well-tolerated and highly effective against different cancer types, and a phase I clinical trial has begun. This talk will provide an overview of the multifaceted applications of NEO100 toward the development and improved delivery of more effective cancer treatments.

Rewiring the Tumor Microenvironment: Could Endocannabinoids Tip the Balance?

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Abstract

Glioblastoma (GBM) is the most lethal primary brain tumor, marked by rapid growth, diffuse invasion, and resistance to therapies. Recent studies emphasize that GBM progression is not solely driven by malignant cells but also by the tumor microenvironment (TME), which shapes immune responses and supports tumor survival. Within TME, GBM-associated microglia are a key non-neoplastic population that promotes tumor expansion, invasion, and immunosuppressive milieu. The interaction between glioma cells and microglia is highly dynamic, involving a network of signaling pathways that reprogram microglial phenotypes toward tumor-supporting functions. Elucidating these mechanisms is critical for identifying novel therapeutic targets. In this study, we investigated the effects of cannabinoid-related molecules on microglia–glioma crosstalk using *in vitro* co-culture models. We focused on the endocannabinoid anandamide (AEA) and the dopamine-derived lipid N-oleoyldopamine (OLDA), testing their activity on murine GBM cell lines (CT-2A and GL-261) and microglial cells (BV2 and C8-B4). Treatments influence reactive oxygen species production, proliferation, and cell viability. Although AEA and OLDA are known ligands for CB1 and TRPV1 receptors, the involvement of these receptors in our system has not yet been directly confirmed. Our preliminary results suggest that cannabinoid-related molecules can modulate microglial behavior in the GBM context, potentially interfering with tumor-supportive functions. These findings support further studies to dissect the molecular pathways involved and assess the therapeutic potential of targeting cannabinoid signaling in GBM. Overall, our work provides evidence that manipulating microglia–glioma interactions via cannabinoid-related compounds may offer a novel approach for GBM therapy.

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