Biomere

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SYMPOSIUM INDEX

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SYMPOSIUM OVERVIEW

We presented our first Biomere West Coast Preclinical Research Symposium at the JOINN Innovation Park in Richmond CA on April 11, 2022. Mark Nedelman, our CEO, moderated the inaugural event. Dr. Guangping Gao, set the stage with a comprehensive review of gene therapy that included detailed insights into a successful clinical program for Canavan's disease. The second speaker, Dr. Harriet Kamendi, shared valuable insights into safety studies required for IND submissions. The next two speakers, Dr. Vito Sasseville and Dr. Mark Milton, covered various modalities for ophthalmic diseases and shared useful considerations for designing nonclinical safety studies in the area. The final speaker, Dr Michael Do, presented interesting research on two circuits that are important for visual acuity and light sensing. The symposium concluded with a panel discussion that centered on two topics: the importance of nonhuman primates (NHPs) in cell and gene therapy studies and specifically ocular studies, and the requirement to suppress the immune system prior to administering gene therapies.

CURRENT GENE THERAPY TRENDS

Dr. Guangping Gao, PhD | Professor in Biomedical Research
University of Massachusetts Medical School

Short Bio

Dr. Gao is the Co-Director of the Li Weibo Institute for Rare Diseases Research, Director, Horae Gene Therapy Center and Viral Vector Core, Professor of Microbiology and Physiological Systems, Penelope Booth Rockwell Professor in Biomedical Research at the University of Massachusetts Medical School. Dr. Gao has focused on molecular genetics and viral vector gene therapy of rare genetic diseases over his 30-year career, and has co-founded several companies including Voyager Therapeutics, that focus on developing AAV gene therapeutics for rare diseases.

Top Keywords

- Gene therapy
- AAV
- NHP models
- Rare diseases
- Metabolic disorders
- Gene replacement

Presentation Summary

In this engaging presentation, Dr. Gao provides an overview of current trends in gene therapy starting with the definitions of in vivo gene therapies and ex vivo modification of patient cells. His research has focused on the in vivo administration of adeno-associated virus (AAV) that has several desired characteristics and is used as a gene therapy delivery system in 13 different disease areas, including diseases of the central nervous system (CNS). The presentation focused on the application of AAV gene therapy in CNS and metabolic diseases and highlighted four major areas - viral vector engineering, manufacturing and QC, vector immunogenicity and the need for large animal models to evaluate gene therapies.

One of the major areas of interest is capsid engineering that can be done through natural evolution, directed evolution and rational engineering. Directed evolution using capsid surface translational panning is the most popular approach where a PCR based methods is used to generate novel capsid protein sequences). In silico design and machine learning based methods are also emerging approaches to engineer capsids. An example of successful high throughput natural sequence selection of capsid proteins was the identification of a novel AAV2 variant (v66) that had increased CNS tropism (13x) and showed sustained expression of AAV delivered transgene both constitutively and with rapamycin induction.

Gene therapy includes four major approaches: gene replacement, gene therapy, gene addition and gene activation. An example of successful gene replacement is Canavan's disease that has a metabolic defect which causes accumulation of NAA (N-acetylaspartate) in white matter resulting in significant neurological issues in children. A gene therapy approach was developed to systemically deliver AAV9 across the blood brain barrier (BBB) to deliver a transgene encoding the missing enzyme to break down NAA in neuronal cell mitochondria. A clinical trial on a single 2-year-old child with Canavan's disease showed high efficacy with good safety profile and most importantly, the child is alive today with a good quality of life.

Vector immunogenicity is a big issue with gene therapies. The mechanism of the immune system reaction to viral vector administration has been studied in some detail. Innate immunity kicks in first with acute toxicity in response to circulating AAV followed by type 1 interferon response, IgM and IgG response followed by complement activation and endothelial activation. There are therapies available to manage innate immunity acute responses that occurs in days.

The adaptive immune response includes cytotoxic T-cell response and the development of neutralizing antibodies. One approach to reduce the adaptive immune response is to design the transgene expression cassette to include APC (antigen presenting cells) specific microRNAs (miRs) that reduce antigen presentation. The miRs are expressed exclusively in APCs and form the RISC (RNA induced silencing complex) that degrades the transgene transcripts in APCs thus reducing the adaptive immune response. Another AAV related toxicity is neurotoxicity in dorsal root ganglia (DRG) that can also be managed via miR detargeting.

NHPs (nonhuman primates) have more translational value than rodents for gene therapy using multiple AAV serotypes including AAV3, AAV8 and AAV9. NHPs are primarily used for safety studies, but due to lack of disease state NHP models, efficacy studies are not typically performed. However, there are exceptions and one example of the use of large animal models is the evaluation of gene therapy for maple syrup urine disease. The gene therapy studies started in cell lines, continued in mouse models and eventually to a bovine model. This disease is fatal if left untreated and the current therapies are either dietary restrictions to reduce branched amino acids or liver transplants. In this gene therapy approach, AAV9 was used to deliver E1alpha and E1beta subunits of branched-chain α-ketoacid dehydrogenase complex (BCKDH) via systemic intravenous administration in a naturally occurring cow model of maple syrup urine disease. The disease phenotype was successfully reversed in the bovine model.

RNA based therapies can be broadly classified as RNA editing, RNA silencing and read through therapy to reverse premature translational termination. AAV based therapies are used to relive premature translation termination by delivering suppressor tRNAs. Suppressor tRNA differs from normal tRNA by one nucleotide and a library of suppressor tRNAs can be developed for different amino acids. It is important to note that the efficacy is typically determined by the delivery efficiency and not the tRNA binding. A successful example of this approach was shown in MPS Type I where suppressor tRNA reads through UAG premature stop codon in alpha-L-iduronidase (IDUA) gene that codes for an enzyme required for the breakdown of GAGs (glycosaminoglycans). The gene therapy was tested in the Hurler mouse model of MPS I where there was an increase in IDUA enzyme activity and corresponding decrease in GAGs after virus administration.

Top Keywords
- IND submission
- Target product profile
- Safety pharmacology
- ADME
- Non-GLP toxicology
- Genotoxicity

BEST PRACTICES NAVIGATING THE IND PROCESS

Dr. Harriet Kamendi, PhD | Consultant

Short Bio

Dr. Kamendi is a consultant working with private companies on chemical risk assessment. She started her career at AstraZeneca where she served as a study director for multiple projects aimed at developing a combined model for screening new drug compounds. After 5 years at Astra Zeneca, she started consulting on environmental chemical risk assessment for private companies and for the state of Maryland. Dr. Kamendi joined Emergent Biosolutions in 2015 where she served as the resident toxicologist and non-clinical development manager. She received her PhD in pharmacology from Howard University and completed postdoctoral training at George Washington University.

Presentation Summary

In this presentation, Dr. Kamendi shares key inputs for an IND submission since there are no established best practices for IND submissions. The objective of nonclinical drug development is to identify the right patient population for the right drug with the right properties dosed at the right dose and time. The first step that needs to be completed before drug product development is building the target product profile (TPP) sheet. The main characteristics of the TPP are: product description including mechanism of action, indication of choice, patient population (gender, age etc.) clinical pharmacology (safety and PK profiles), dosing and administration, and marketability that includes reach, competitors, alternatives and market penetration. Some of the other key considerations are efficacy including physical properties of drug that can help narrow down the compounds to move forward with, in vitro & in vivo ADME, secondary pharmacology including organ specific toxicology. An example of in vitro ADME is the evaluation of drug metabolism in hepatocytes or microsomes from various species including humans, NHPs, dogs, rats, mice and, if available, mini pigs. This data will help drug developers identify which animal model closely resembles human drug metabolism including ADME and pharmacokinetics. Drug distribution studies are required to understand where the drug tends to accumulate in the body. Tolerability is important especially for systemic delivery routes including intravenous, intramuscular, subcutaneous or topical delivery. Target meditated toxicity involves short term and long-term toxicity studies to identify the sweet spot for efficacious dosing and acceptable toxicity. Lastly, secondary pharmacology studies identify off target binding and cardiovascular effects mediated by hERG and other ion channels.

Non-GLP toxicology programs typically require clinical observations of drug effects with macroscopic examination of organs in 2 species. Safety pharmacology including cardiovascular assessment, respiratory assessment and CNS assessment should be done before GLP tox studies, so data from non-GLP tox and safety pharmacology studies are used to plan GLP toxicology studies. In the event that a drug needs to be dosed more than once, repeat dosing studies require clinical dosing at specific duration and evaluation of tolerance at administration site along with immune toxicology and reproductive toxicology. Genotoxicity is the assessment of chromosomal damage and are critical data to ensure that the program can move into the clinic without major liabilities. It is important to note that once the pharmacology and toxicology studies are completed, the IND can be filed but nonclinical studies including carcinogenicity studies, abuse liability studies etc. will need to continue. Specifically, for systemic and local administration of gene therapy, it is necessary to evaluate the systemic effect of the transgene before proceeding with full toxicology studies.

THE DESIGN, CONDUCT, & INTERPRETATION OF NONCLINICAL OPHTHALMOLOGY STUDIES ENSURING REGULATORY SUCCESS

PART ONE: LOW MOLECULAR WEIGHT MOLECULES & BIOTHERAPIES

Dr. Vito Sasseville,
DVM, PhD, Dipl. ACVP | PCS Therapeutic Area Head, Ophthalmology & NITD, Novartis Institutes for BioMedical Research

Top Keywords
- Intravitreal injection
- Large animal models
- Ocular toxicity
- Age related macular degeneration
- Dry eye disease

Short Bio

Dr. Vito Sasseville is currently the Preclinical Safety Therapeutic Area Head for Ophthalmology and the Novartis Institute for Tropical Diseases. He joined the Novartis Institutes of Biomedical Research as Global Head of Discovery Pathology in 2011 after working at Bristol-Myers Squibb and Millennium Pharmaceuticals (Takeda) in the Drug Safety groups. Dr. Sasseville received his D.V.M. from Tufts University and Ph.D. from The University of Connecticut. He obtained board certification in Anatomic Veterinary Pathology and conducted his postdoctoral research and served as an Assistant Professor in the Department of Pathology, Harvard Medical School investigating the molecular mechanisms of Simian Immunodeficiency Virus-induced encephalitis before transitioning to industry.

Presentation Summary

In the first presentation on nonclinical ophthalmology studies, Dr. Sasseville focused on key considerations for low molecular weight therapies. Over 2 billion people have vision impairment globally caused by several diseases including cataracts, dry eye disease, diabetic retinopathy, glaucoma and age-related macular degeneration. Age-related macular degeneration (AMD) has discrete stages – early (often asymptomatic), intermediate and late (10% develop wet or neovascularized or dry). About 90% of AMD patients end up with vision loss. 5 approved therapies are available for wet AMD that target VEGF. Wet AMD is multi-factorial and treatments vary depending on underlying causes but it is important to note that there are no approved therapies for dry AMD. Dry eye disease is also multi-factorial and multiple therapies are available. Another class of diseases that cause vision loss are inherited retinal diseases and over 250 genes have been implicated in disease development.

There are multiple routes of administration for ocular therapies and intravitreal administration is the most common, while intracameral is preferred for low molecular weight therapies. Topical, subconjunctival and suprachoroidal are other routes for low molecular weight therapies while subretinal delivery is preferred for gene therapies. Approved ocular drugs include several modalities including antibody fragments, fusion proteins, aptamers, small molecules (for glaucoma and dry eye disease) and gene therapies. Preclinical safety studies for ocular therapies include 4 major studies: identification of relevant animal model species, routes of administration, study duration and frequency of dosing. The standard approach of 2 non-rodent species is used such as rabbit and

NHP or rabbit and dog. For biotherapeutics, NHPs may be the only option as rabbits show high immunogenicity. Two routes of administration are tested including the preferred ocular route that will be used in the clinic and systemic administration. The duration of the study should match or exceed clinical trial duration and are typically 6-9 months studies while systemic studies can can be shorter (1-3 months). The frequency of dosing will be determined by whether clinically effective dose exceeds toxicology dose but max clinical dose should be met or exceeded if possible.

Endpoints in ocular studies focus on structural and functional assessments including examination of eye structures, measurement of retinal thickness & intraocular pressure, and imaging endpoints. However, preclinical endpoints may no translate to the clinic as typical clinical endpoints are visual acuity measurements. Ocular toxicity caused by systemic delivery are uncommon, but can be a major hurdle if observed as side effects can include cataracts, edema, degeneration and neuritis. Localized toxicology in the ocular region is common and needs to be analyzed to understand the causative factors.

THE DESIGN, CONDUCT, & INTERPRETATION OF NONCLINICAL OPHTHALMOLOGY STUDIES ENSURING REGULATORY SUCCESS

PART TWO: GENE & CELL THERAPIES

Dr. Mark Milton, MSc, PhD | Global Head Gene Therapy Therapeutic Area, Novartis Pharmacokinetic Sciences

Top Keywords
- Gene therapy
- AAV
- Ocular toxicity
- Biodistribution

Short Bio

Dr. Mark Milton is the Global Head of the Gene Therapies Therapeutic Area in the Pharmacokinetic Sciences Department at Novartis where he oversees the immunogenicity, biodistribution, and shedding of Gene Therapies. Prior to joining Novartis in Jan 2009, Mark worked at GD Searle, Millennium Pharmaceuticals, and Tempo Pharmaceuticals. At Novartis Mark has provided leadership in ocular PK/IG, the PK/PD/IG of Biologics, and Gene Therapies. He was the past-chair of the BioSafe PKPD EWG, a member of the BioSafe LC, IQ Board of Directors, a member of the AAPS pre-existing antibody and Immunogenicity Risk Assessment Working Groups, and was the BIO observer to the ICHS3A Q&A WG. Mark received his undergraduate degree in Biochemistry and Soil Science from UCNW, Bangor, master's degree in Toxicology and Ph.D. in Biochemical Toxicology from the University of Surrey, England.

Presentation Summary

In the second presentation on nonclinical ophthalmology studies, Dr. Milton focused primarily on in vivo gene therapies. The ideal target cell for gene therapy is a slow dividing cell to maximize the presence and therapeutic effect in target cells as it is challenging to get sufficient gene therapy into target cells with acceptable side effects. Gene therapies for ocular diseases typically use AAVs that are delivered intravitreally

or subretinally. Cell therapies can be encapsulated in a device that can be implanted intravitreally but this has had limited success. Some important CMC considerations are the dose concentration, low endotoxin levels, minimal empty capsids and particulate matter and ensuring that the transgene is compatible with the viral vector delivery system.

The FDA has published guidance for inherited retinal diseases that can be applied for other ocular diseases. Ocular gene therapies are typically dosed once so it is critical to use the right dose using a reasonably efficacious and safe route of administration while identifying and mitigating toxicity. There are few good pharmacology models to test gene therapies for ocular diseases and it is important to remember that NHPs do not mount an immune response to AAV capsids. Biodistribution studies are required to assess the distribution, persistence and clearance of the viral vector and evaluate transgene expression levels at site of administration and systemically in the blood.
The distribution of vectors is somewhat predictable: vectors delivered to ocular tissues concentrate in the ocular and CNS tissues and have low systemic concentrations. Consequently, viral shedding should be evaluated in tears but that may not be possible in some animal models. Tox studies for gene therapies should have a duration of 6 months and evaluate dose range, route of administration and measure clinically relevant endpoints.

The overall nonclinical plan should be lean, follow 3Rs and don't necessarily do things out of an abundance of caution. Dr. Milton presented an interesting case study on the evaluation of an AAV8 vector carrying the RLBP1 transgene that highlighted the key considerations for nonclinical studies.

Lastly, there are some active investigator-initiated cell therapy studies that are not under the FDA oversight but it is important to note that cell therapies are likely going to be recognized as foreign in animal models so studies will need to be done in immunosuppressed models that may not be physiologically relevant.

Top Keywords

- Circadian clock
- Intrinsically photosensitive retinal ganglion cells
- Melanopsin
- Nonimage vision
- Age related macular degeneration

VISUAL SPECIALIZATIONS WITHIN & ACROSS SPECIES

Michael Tri Do | Associate Professor, Harvard Medical School and Boston Children's Hospital

Short Bio

Dr. Michael Do is an Associate Professor at Harvard Medical School and Boston Children's Hospital. Mike obtained his PhD in Neurobiology at Harvard Medical School and completed his post-doctoral training at Johns Hopkins University in 2011. The research focus of Dr. Do's lab is to understand how light drives visual perception and the setting of the internal body clock.

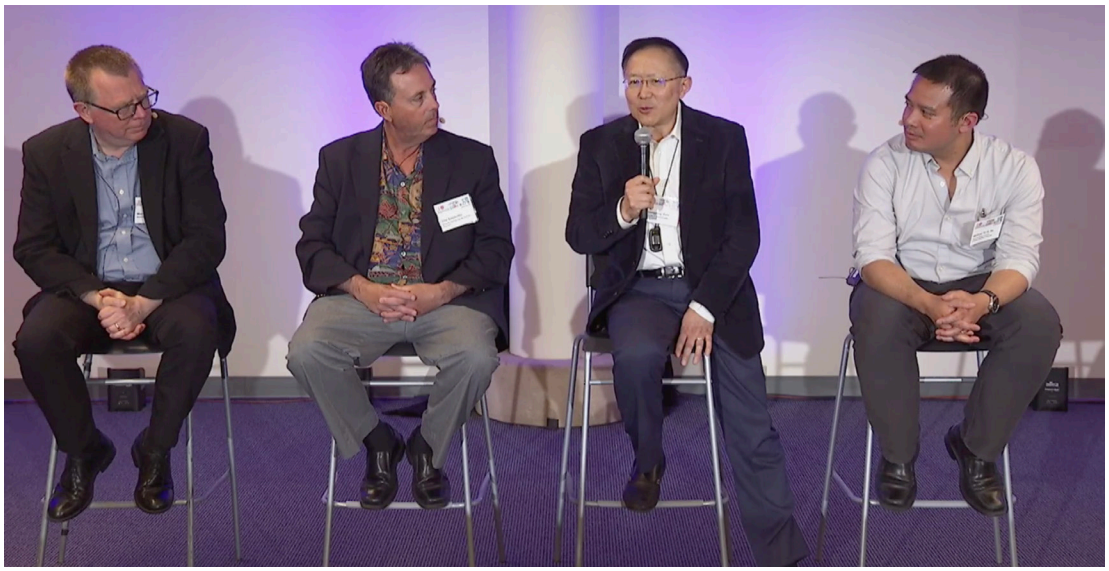
Presentation Summary

In this basic science presentation, Dr. Do discusses the key role of intrinsically photosensitive retinal ganglion cells (ipRGCs) to process light signals and highlights the tristable states of melanopsin pigment that is critical for the circadian clock and nonimage vision.

Image vision recognizes objects and nonimage vision to sense overall light intensity for circadian function, sleep, pupillary and hormonal regulation. Rods and cones express visual pigments that initiate downstream signaling in response to light resulting in an electric response that is transported to retinal ganglia cells through the optic nerve. ipRGCs process light either through rods and cones or independent of rods and cones to transmit signal to drive pupil dilation, circadian clock, melatonin expression, photophobia, pain etc. and the ablation of ipRGCs removes most light responsive functions. Melanopsin has 3 states – melanopsin R (only state in darkness), metamelanopsin M (active state) and extramelanopsin (E) and, at any given time, there is a mix of melanopsin states. Melanopsin is required to manage responses to light and is expressed in multiple animals including lower species like fishes. The various melanopsin activation states have clinical implications to manage the circadian clock in dark settings.

Humans and primates have highest visual acuity and contrast resolution and this is due to the fovea that is only present in humans and primates. The fovea is located in the center of the macula where there is a high density of cones that degenerate in AMD. Therefore, replacement of foveal cones in age related macular degeneration could be an option for cell therapies.

OPHTHALMOLOGY DISCUSSION PANEL



Dr. Mark Milton, Dr. Vito Sasseville, Dr. Guangping Gao, Dr. Michael Tri H. Do

HIGHLIGHTS OF THE PANEL DISCUSSION

Panelists: Guangping Gao, Vito Sasseville, Mark Milton, Michael Tri H. Do

The panel discussion covered a few interesting topics: the importance of NHPs in drug development and ocular studies, the need to suppress the immune system prior to administering gene therapies and the importance of adopting new technologies to advance gene therapies.

The key discussion points around the use of NHPs are summarized below:

- The cost and availability of NHPs is impacting drug development. In the past 2 years, costs have quadrupled and the origin of the models can have an impact due to differences in seropositivity levels and transduction efficiency.
- Published literature suggests that the source of NHP models does matter and natural history studies need to be done before using NHPs from different origins.
- It is preferable not to mix animals from different sources in a specific study.
- It will be important to rethink about the study design using NHPs and perhaps consider reduced dosing.
- One option is to administer the IdeS enzyme to cleave IgGs prior to AAV administration to create a window where there is reduced immunogenicity. However, it is possible that pre-existing anti-AAV antibodies can be redistributed in response. Additionally, IdeS may not work in monkeys, so an ortholog for the currently available enzyme may need to be used

- Another consideration is that NHP colonies may be too clean resulting in low antibody titers so for some studies wild caught animals may be more suitable.

- It is not advisable to treat NHPs with steroids prior to performing proof of concept studies, but it is common practice to prophylactically administer steroids out of an abundance of caution. This is typically not required for ocular studies.

A summary of the responses to an audience question: how translatable are NHP data to humans?

- There are some qualitative similarities between macaque and humans that are not there in other species. Macular degeneration studies can only be done in a species that has a macula. can be difficult to find orthologs between rodents and macaques for specific cell types.

- If a test article is highly toxic in NHP models, it won't go into the clinic so we won't know if that is a false signal. The type of test article (small molecule vs biotherapeutic vs gene therapy), route of administration and the in-life and necropsy & histopathology observations are key inputs in determining if the drug will move into the clinic. If the degree of inflammation is very over, then the drug would not go into the clinic.

A summary of the responses to an audience question: does immunosuppression by prophylactic steroids enhance innate immunity to AAV treatment?

- Use of steroids are not immunosuppressive but it may impact innate immune response without affecting the humoral response. If you want to suppress treatment induced immune response, then rituximab will need to be used but that is heavy and dose is not clear.

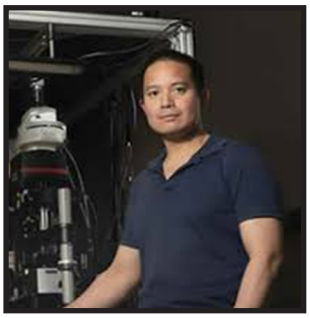
- Ocular studies do not have any immunomodulation. However, every CRO has SOPs on veterinary intervention when inflammation is too high. If there is a marginal call, sponsor has to discuss with lab veterinary staff to balance ethics and need to get therapies to patients and decide if animals need to be taken down from the studies. If animals respond well to steroid pretreatment, that is good news for patients.

A summary of the comments in response to an audience question: what are the applications of new and emerging technologies – imaging and MS in ocular studies?

- Techniques like MALDI have been mentioned in presentations. In gene therapies, distribution is done based on PCR but I am pushing towards MALDI. The advantage is that can look for capsid and transgene expression. Using technologies to look at distribution at the cellular level will be critical as tissues will have heterogeneous distribution within a specific organ.

- For many gene therapy companies, new technology called MERFISH that is single cell RNA sequencing coupled with 2D localization. This is similar to MALDI at the mRNA level.

- The field needs to stop doing traditional methods and invest more time in new techniques and framing questions better.



OCULAR WEBINAR
ORIGINS OF EXTRAORDINARY VISUAL ACUITY IN PRIMATES

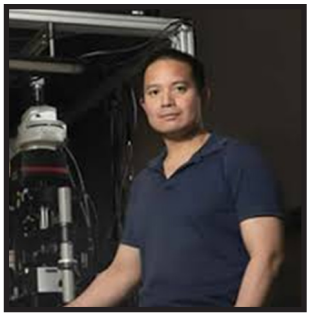
Michael Tri Do | Associate Professor, Harvard Medical School and Boston Children's Hospital

Top Keywords
- Macular degeneration
- Fovea function
- Fovea anatomy

Short Bio
Dr. Michael Do is an Associate Professor at Harvard Medical School and Boston Children's Hospital. Mike obtained his PhD in Neurobiology at Harvard Medical School and completed his post-doctoral training at Johns Hopkins University in 2011. The research focus of Mike's lab is to understand how light drives visual perception and the setting of the internal body clock.

Webinar title
Origins of Extraordinary Visual Acuity in Primates

Webinar abstract
In this webinar, Dr. Gao presents a comprehensive overview on the key principles, history, current challenges, and future directions of human gene therapy with a focus on AAV gene therapy for rare diseases. The webinar also showcases AAV capsid engineering to modulate target tissue tropism and biodistribution and includes examples of using AAV for gene replacement, gene addition, gene silencing and *in vivo* gene editing in preclinical studies. Additionally, strategies to overcome immunological barriers to improve the efficacy of AAV-mediated gene therapy are reviewed.



OCULAR WEBINAR
SENSING LIGHT FOR PHYSIOLOGICAL CONTROL

Michael Tri Do | Associate Professor, Harvard Medical School and Boston Children's Hospital

Top Keywords
- Retinal ganglion cells
- Depolarization
- Iprgc discovery
- Iprgc melanopsin

Short Bio

Dr. Michael Do is an Associate Professor at Harvard Medical School and Boston Children's Hospital. Mike obtained his PhD in Neurobiology at Harvard Medical School and completed his post-doctoral training at Johns Hopkins University in 2011. The research focus of Mike's lab is to understand how light drives visual perception and the setting of the internal body clock.

Webinar title

Sensing Light for Physiological Control

Webinar abstract

In this webinar, Dr. Do describes the structure and function of intrinsically photosensitive retinal ganglion cells (ipRGCs) in mouse and primate eyes focusing on tuning of the cells to specific light intensities. This work demonstrates an important depolarization block as light intensity increases highlighting the precise firing of the ipRGCs for rapid decoding of irradiance.

WEBINAR SERIES
NOVEL APPROACHES IN CELL AND GENE THERAPIES

Introduction
Rapid advancements in the development of novel cell and gene therapies have been powered by technological innovations in gene delivery and viral engineering. One of the big challenges in the gene therapy space is the immune response to vectors that has short- and long-term consequences, so it is critical to engineer gene therapy vectors to overcome the neutralizing antibody response. Another area of rapid growth is stem cell therapy space and promising therapies are being developed in several disease areas including eye diseases and neurodegenerative diseases.

In this webinar series, we highlight the key principles of virus mediated gene therapy and the development of novel cell therapies. The webinars showcase multiple approaches to viral vector development including strategies to overcome the neutralizing immune response, and highlights the development of novel cell therapies for the central nervous system and Parkinson's disease.

WEBINAR SERIES
GENE THERAPY FOR RARE DISEASES – A NEW PARADIGM IN MEDICINE

Guangping Gao | Professor, University of Massachusetts Medical School

Top Keywords
- Gene therapy
- AAV
- AAV capsid
- Rare diseases

Short Bio
Dr. Gao is the Co-Director of the Li Weibo Institute for Rare Diseases Research, Director, Horae Gene Therapy Center and Viral Vector Core, Professor of Microbiology and Physiological Systems, Penelope Booth Rockwell Professor in Biomedical Research at the University of Massachusetts Medical School.

He was elected as a fellow of the US National Academy of Inventors and American Academy of Microbiology and is the outgoing President of the American Society of Gene and Cell Therapy. He was ranked #4 in the World Top 20 Translational Researchers in 2018 by Nature Biotechnology.

Dr. Gao has focused on molecular genetics and viral vector gene therapy of rare genetic diseases over his 30-year career, and has co-founded several companies including Voyager Therapeutics, that focus on developing AAV gene therapeutics for rare diseases.

Webinar title
Gene Therapy for Rare Diseases – A New Paradigm in Medicine

Webinar abstract
In this webinar, Dr. Gao presents a comprehensive overview on the key principles, history, current challenges, and future directions of human gene therapy with a focus on AAV gene therapy for rare diseases. The webinar also showcases AAV capsid engineering to modulate target tissue tropism and biodistribution and includes examples of using AAV for gene replacement, gene addition, gene silencing and *in vivo* gene editing in preclinical studies. Additionally, strategies to overcome immunological barriers to improve the efficacy of AAV-mediated gene therapy are reviewed.

WEBINAR SERIES
STRATEGIES FOR IN VIVO BARRIERS TO GENE THERAPY VECTORS

Casey Maguire | Associate Professor of Neurology, Harvard Medical School

Top Keywords
- Gene therapy
- AAV
- AAV vector
- AAV capsid
- Gene delivery
- Microvesicles
- Extracellular vesicles

Short Bio
Dr. Casey Maguire is currently an Associate Professor of Neurology at Harvard Medical School and an Investigator at the Massachusetts General Hospital (MGH). Casey received his PhD from the University of Rochester Medical School. He has been at MGH since 2006 starting with a post-doctoral fellowship followed by Instructor and Assistant Professor positions. His research focuses on improving virus vectors to allow effective human gene therapy in the face of delivery and immune-related barriers.

Webinar title
Strategies for in vivo barriers to gene therapy vectors

Webinar abstract
In this webinar, Dr. Maguire discusses technological innovation of AAV (adeno-associated virus) vectors to overcome challenges associated with AAV vector delivery to target organs and immune evasion. His talk focuses on two innovative approaches to improve AAV gene delivery to the central nervous system (CNS). The first approach is screening AAV capsid libraries using *in vitro* and *in vivo* models to identify and validate clones that have enhanced delivery to the CNS. The second approach uses extracellular vesicles or microvesicles to deliver AAVs more efficiently to multiple organs including the brain, eye, liver and inner ear.

WEBINAR SERIES
RETARGETING AND SHIELDING MEASLES VIRUS VECTORS FOR ONCOLYTIC VIROTHERAPY

Miguel Muñoz-Alía | Research Associate, Mayo Clinic

Top Keywords
- Gene therapy
- Measles
- Oncolytic virus
- Measles vaccination

Short Bio

Dr. Muñoz-Alía is a Research Associate in the Department of Molecular Medicine at the Mayo Clinic. He received his PhD in Cell Biology and Genetics at Autonomous University of Madrid, Spain, after completing his bachelor's degree in Biology. He began his career at Spanish National Reference Laboratory for Measles and Spanish National Center for Biotechnology, where he acquired a keen interest in molecular epidemiology and evolution of measles virus genotypes. In 2015, he joined the Mayo Clinic where he is working on the clinical development of oncolytic measles viruses.

Webinar title

Retargeting and Shielding Measles Virus Vectors for Oncolytic Virotherapy

Webinar abstract

In this webinar, Dr. Muñoz-Alía discusses how the measles virus can be engineered to specifically attack tumors as an oncolytic virus (OV). One of the primary challenges with using the measles virus as an OV is the presence of neutralizing antibodies due to the measles vaccination in childhood.

In order to efficiently target the measles virus to specific tumors, viral envelope proteins from the canine distemper virus are inserted to replace the measles virus membrane fusion proteins. This gene therapy approach showed efficient transduction of tumor cells while avoiding the neutralizing antibody response in myeloma and ovarian cancer animal models.

WEBINAR SERIES
REGENERATIVE STRATEGIES IN THE CENTRAL NERVOUS SYSTEM

Molly Shoichet | University of Toronto

Top Keywords
- Hydrogel
- Age related macular degeneration
- Amd eye
- Retinitis pigmentosa treatment
- Stroke damage
- Cell therapy for blindness

Short Bio

Professor Molly Shoichet holds the Tier 1 Canada Research Chair in Tissue Engineering at the University of Toronto. Her research is focused on drug and cell delivery strategies in the central nervous system and 3D hydrogel culture systems to model cancer, and she has also co-founded four spin-off companies. Dr. Shoichet is the recipient of many prestigious distinctions and the only person to be inducted into all three of Canada's National Academies of Science, Engineering and Health Sciences. Additionally, she is a Fellow of the Royal Society and Foreign Member of the US National Academy of Engineering. Dr. Shoichet received her Bachelor's degree from MIT and her PhD from the University of Massachusetts, Amherst in Polymer Science and Engineering.

Webinar title

Regenerative Strategies in the Central Nervous System

Webinar abstract

In this 2-part webinar, Dr. Shoichet discusses two methods of cell regeneration in the CNS – one method is a cell transplantation in the retina and the other method is the stimulation of endogenous stem cells to replace neurons after a stroke.

The cell transplantation in the eye is a method where PR (photoreceptor) and RPE (retinal pigment epithelium) cells in a hyaluronan-methylcellulose hydrogel are injected subretinally into two mouse models of blindness. Injection of both PR and RPE cells in the hydrogel resulted in improved vision, and the hydrogel prevented cell clumping and also had an anti-inflammatory effect. This cell therapy for blindness could be potentially used as an age-related macular degeneration therapy or retinitis pigmentosa treatment.

In the second segment, Dr. Shoichet describes a less invasive strategy to stimulate endogenous stem cells to differentiate into neurons after stroke damage. An osmotic minipump is used to deliver therapeutics like cyclosporine A and erythropoietin in the hydrogel to repair cell damage and induce tissue regeneration. The delivery of known stem cell differentiators in the hydrogel was shown to improve tissue regeneration and function in mouse and rat models of stroke.

WEBINAR SERIES
CHAMELEON'S EVADER TECHNOLOGY: A MORE POTENT AAV VECTOR WITH LESS IMMUNE RESPONSE

Jeffrey Vick | Chief Business Officer, Chameleon Biosciences

Top Keywords
- Gene therapy
- AAV
- AAV vector
- Gene delivery
- Immune response

Short Bio

Jeffrey Vick is a co-founder and chief business officer at Chameleon Biosciences, an early stage gene therapy company that is developing a proprietary vector platform EVADER. Jeff has more than 25 years of senior management experience in the global biopharmaceutical industry and has particular expertise in Gene Therapy. He has led the Business development and IP groups at Genethon and Gencell and has also led multiple collaborations with companies like Audentes and GenSight. Jeff has also worked as a venture capitalist where he founded, grew and sold multiple companies, and also served as the CEO of Silence Therapeutics. He earned an MBA from Stanford University following a Master's degree in Chemistry from UC San Diego and a Bachelor's degree in Chemistry from the University of Virginia.

Webinar title

Chameleon's EVADER technology: a more potent AAV vector with less immune response

Webinar abstract

In this webinar, Jeff discusses Chameleon's EVADER™ gene therapy platform that is designed to evade the immune system, thus overcoming the neutralizing immune response, expanding the treatable patient population and supporting multiple dosing. The platform envelopes AAVs in a lipid bilayer with specific immune cell inhibitors and is shown to have increased infectivity, delivery and transgene expression in preclinical models. The EVADER™ platform is currently being used to develop gene therapies for multiple diseases in partnership with biotech and pharma companies.

WEBINAR SERIES
BIOANALYSIS OF LARGE MOLECULE THERAPIES

Introduction
Bioanalytical studies are an integral part of pharmacokinetics (PK) and pharmacodynamics (PD) studies, as well as the evaluation of drug toxicity. Typically, an array of methodologies is used to obtain a comprehensive profile of the behavior of the therapy in a systemic biology model. Bioanalysis of large molecule therapies is an evolving area with unique requirements and challenges.

In this 2-part webinar series, experienced bioanalysis scientists highlight the needs and challenges of regulated and non-regulated bioanalysis of therapies with a focus on large molecule drugs. The webinars include a review of bioanalytical methods including ligand binding assays and immunogenicity assays.

WEBINAR SERIES
LARGE MOLECULE BIOANALYSIS: CONCEPTS, TOOLS AND CHALLENGES

Franklin Spriggs | Primary Consultant, Spriggs Bioanalytical Consulting LLC

Top Keywords
- Bioanalysis in drug discovery and development
- Large molecule bioanalysis
- PK bioanalysis
- Ligand binding assays
- Types of ligand binding assays

Short Bio
Franklin Spriggs is a bioanalytical scientist and primary consultant at Spriggs Bioanalytical Consulting LLC. Frank joined Pfizer at the Groton, Connecticut site in 2007 where he became active in the AAPS organization, holding positions in the BIOTEC and Regulatory Sciences sections. In 2015, he received his master's degree in Regulatory Affairs and Quality Assurance from Temple University and then spent 5 years at CROs, working at AIT Bioscience and KCAS Bioanalytical and Biomarker Services.

Webinar title
Large Molecule Bioanalysis: Concepts, tools and Challenges

Webinar abstract
In this webinar, Franklin introduces the basic concepts of bioanalysis including the important role of bioanalysis in successful drug development and reviews currently used plate based and non-plate based assay methods to analyze large and small molecule therapies. He highlights some of the requirements and challenges associated with the bioanalysis of large molecule therapies including antibody-drug conjugates (ADCs), bispecific monoclonal antibodies (mAbs) and protein replacement therapies.

WEBINAR SERIES
ASPECTS OF REGULATED BIOANALYSIS

Andrea Wakefield | Bioanalysis Consultant

Top Keywords

- Bioanalysis in drug discovery and development
- Large molecule bioanalysis
- PK bioanalysis
- Ligand binding assays
- Types of ligand binding assays
- Anti-drug antibodies

Short Bio

Andrea Wakefield is an experienced bioanalytical scientist and independent consultant. Andrea has over 15 years' experience at biotechs and CROs including Alexion Pharmaceuticals, IBEX Pharmaceuticals and Charles River Laboratories. She has supported multiple INDs, clinical trial applications and market authorizations and has experience in gap assessment and mitigation, as well as providing bioanalytical solutions for rare disease therapy development. She obtained her Bachelor's degree with Honors from the University of Ottawa and completed her Master's degree at the University of New Brunswick.

Webinar title

Aspects of Regulated Bioanalysis

Webinar abstract

In this webinar, Andrea focuses on the importance of ligand binding assays in the bioanalysis of small and large molecule therapies and highlights the role of orthogonal assays such as LC-MS to complement the data from ligand binding assays. She discusses preclinical, nonclinical (GLP) and clinical assay development and design including the development of immunogenicity assays and the detection of anti-drug antibodies (ADAs). The importance of bioanalysis data is highlighted with a case study on the development of a therapy for a pediatric rare disease.

KEYNOTE WEBINAR
LEAVING NO DRUG BEHIND

Patrick Dixon | Author, Physician and Futurist, Chairman of Global Change Ltd.

Top Keywords
- Drug discovery and development
- Drug development
- Artificial intelligence
- Anti-aging
- Pharmacogenomics

Short Bio
Dr. Patrick Dixon is a renowned author, physician and futurist. He has consulted extensively with large pharmaceutical companies, and had also founded Virttu Biologics, an oncolytic virus biotech. Patrick is the chairman of Global Change Ltd, a leading growth strategy and forecasting company and has been ranked as one of the 20 most influential business thinkers alive today.

Webinar title
Leaving No Drug Behind

Webinar abstract
In this 5-part webinar, Patrick discusses several topics that are highly relevant in the drug discovery and development space.

- In the first segment, Patrick highlights the need for innovation and collaboration between pharma companies and CROs that have specialty expertise in medtech and infotech, to improve clinical success rates and increase the speed to market, especially for therapies relevant to COVID-19.
- In the second segment, he explores seven mechanisms of aging that are sources for druggable targets for anti-aging therapies, and highlights the healthcare and economic impact of an aging population.
- In the third segment, Patrick discusses the impact of recent technologies such as CRISPR gene editing and whole genome sequencing and the critical role of the microbiome on disease management and drug development.
- In the fourth segment, he shares examples on how AI (artificial intelligence) is being used to more accurate diagnose and monitor therapeutic response.
- In the final segment, he tackles a challenging topic – the high cost of drug development that can preclude promising drugs from being commercialized and limits access to therapies. He predicts that drug development costs will fall partly due to the rapid growth of biosimilars and low cost of generic drug manufacturing.

KEYNOTE WEBINAR
THE FUTURE OF HEALTH, BIOMEDICINE AND LIFE SCIENCES: WHERE CAN TECHNOLOGY TAKE US?

Daniel Kraft | Physician-scientist, Inventor, Entrepreneur, and Innovator

Top Keywords

- Biomedicine
- Artificial Intelligence
- Medical apps
- Digital Health

Short Bio

Dr. Daniel Kraft is a Stanford and Harvard trained physician-scientist, inventor, entrepreneur, and innovator. With over 25 years of experience in clinical practice, biomedical research and healthcare innovation, Daniel has chaired the Medicine for Singularity University since its inception in 2008, and is founder and chair of Exponential. Daniel received undergraduate degrees from Brown University and completed medical school at Stanford. After completing his residency at Massachusetts General Hospital & Boston Children's Hospital, and fellowships in hematology, oncology and bone marrow transplantation at Stanford, Daniel was Board Certified in both Internal Medicine & Pediatrics.

Webinar title

The Future of Health Biomedicine and Life Sciences: Where Can Technology Take Us?

Webinar abstract

In this 2-part webinar, Daniel Kraft discusses the crucial impact of technological innovations on improving healthcare and drug development. In the first segment, he explores the power of exponential thinking to reimagine healthcare and medical research, in combination with the continuous development of medical apps and devices to support end to end patient care, digital health and accelerate drug discovery and development. In the second segment, Daniel discusses novel approaches in drug development including:

- Leveraging pharmacogenomics to design smarter clinical trials and develop personalized therapies
- Using artificial intelligence or AI to improve diagnosis and prognostic monitoring of therapeutic response
- Collaboratively using AI in conjunction with traditional scientific methods to accelerate drug development
- Novel methods of targeted drug delivery

MODERATOR: **Anjli Venkateswaran, PhD**

Short Bio

Dr. Anjli Venkateswaran is an experienced consultant with 20 years' experience in the life sciences and preclinical drug discovery industry, including 3 years in corporate development and 10 years in product management and strategic marketing. She has held positions of increasing responsibility at 5 different organizations including marketing and strategic partnerships at Charles River Laboratories, and strategic marketing at a venture funded cancer diagnostic company. Anjli started her career at Cell Signaling Technology as a scientist and transitioned to sales and product management roles. She received her doctoral degree in Biochemistry from the Ohio State University.