RARE METABOLIC DISORDERS
DETECTION, RESEARCH, MANAGEMENT AND TREATMENT

ABSTRACTS

20th - 22nd September 2016
London, UK
This summit will discuss the ever-growing field of research surrounding metabolic disorders, metabolomics and therapies. From congenital disorders to inherited metabolic diseases, this event will investigate the cutting-edge developments in an informal academic setting, in an atmosphere conducive to debate and discussion.

With a number of sessions over three days, many aspects of the metabolome will be covered, bringing together those working in academia, medicine, biotechnology and pharmaceuticals.

This event has CPD accreditation

This abstract book will be finalised two weeks before the event

www.lifescienceevents.com/Metabolism2016
# Table of Contents

Invited Speakers Abstracts ........................................................................................................ 5
Role and regulation of the RNA-binding protein Bicc1 in cystic kidney diseases .................. 5
Mobile application for balance training, in people with familial dysautonomia: three case reports ....... 5
Autonomic Dysfunction in Familial Dysautonomia .................................................................. 5
Recent Advances in the Treatment of Mitochondrial Ophthalmic Diseases ......................... 5
B12 deficiency and Gestational diabetes – an update ............................................................... 5
Biochemical insights into Primary hyperoxaluria type III ....................................................... 6
Enzyme replacement therapy for lysosomal storage disorders: the pharmacology of marginal gains .... 6
Managing Familial Dysautonomia in a North London DGH: A paediatrician's steep learning curve ............ 6
Alkaptonuria - Metabolic response to treatment with Nitisinone ............................................ 6
Computational approaches to targeted drug design in metabolic diseases .............................. 6
GRK2 as a new integrative node in obesity and insulin resistance: multi organ effects ............... 6
Respiratory Problems in Familial Dysautonomia .................................................................... 7
The impact of genomics on rare disease research ................................................................. 7
Familial Dysautonomia: Genotype, Phenotype and Translational Research ............................ 7
Neurometabolic Disorders in Children ..................................................................................... 7
The role of Open Innovation in development of new therapies for rare diseases .................... 7
   Professor Shamima Rahman, ............................................................................................. 8
Next Generation Sequencing (NGS) approach to discovery of rare neuro-metabolic disorders ...... 8
DevelopAKUre: a patient-led clinical trial for a rare disease ..................................................... 8
Circulating microRNAs as markers of the liver neoplastic process in a mouse model of hereditary tyrosinemia .......................................................................................................................... 8
Steroid profiling for rare diseases ............................................................................................ 8
Treatable Neurometabolic Diseases in the 21st Century .......................................................... 9
Biliary transporter mutations; implications for gestational liver disease ................................... 9
Day 1: ........................................................................................................................................ 9
   Oral Presentation Abstracts ................................................................................................. 9
Day 2: ........................................................................................................................................ 9
   Oral Presentation Abstracts ................................................................................................. 9
THE USE OF PHENOMICS IN THE DIAGNOSIS, TREATMENT AND POTENTIAL TREATMENT OF LAMINOPATHIES .......................................................... 9
Day 3: ........................................................................................................................................ 10
   Oral Presentation Abstracts ................................................................................................. 10
CHOLIC ACID THERAPY IN ZELLWEGER SPECTRUM DISORDERS ................................ 10
Role and regulation of the RNA-binding protein Bicc1 in cystic kidney diseases
Professor Daniel Constam, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland
Renal cysts in autosomal dominant polycystic kidney disease (ADPKD) are induced by impaired calcium flux leading to elevated cAMP and mTOR signaling and a switch from oxidative glucose phosphorylation to glycolysis, but how calcium regulates these pathways is unclear. We found that cAMP signaling is inhibited by the RNA-binding protein BICC1 and its phosphorylation by calcium-dependent CaMKII. Furthermore, genetic and biochemical analysis revealed a regulatory interaction of BICC1 with Inversin, the protein mutated in the related cystic disease nephronophthisis type 2. Regulation of BICC1 emerges as a potential new target for future therapies to program the metabolism of epithelial cells.

Mobile application for balance training, in people with familial dysautonomia: three case reports
Mrs Rosalee Gefen, The Zinman College of Physical Education & Sport Sciences, Wingate Institute, Netanya, Israel
Familial dysautonomia (FD) is a rare genetic autosomal recessive disease that impairs vital functions and causes neural, skeletal and motor deficits. Osteoporosis coupled with deficits in static and dynamic instability, results in a high risk for falls and significant physical impairment. Active balance rehabilitation training for people with FD poses significant challenges, for our case study an iPhone application was developed and used in training three young adults with FD. The Berg balance test and the FSST were conducted before training, after training and two months after follow up without training, with two patients exhibiting improvement on both measures.

Autonomic Dysfunction in Familial Dysautonomia
Dr Ellen Merete Hagen, Consultant Neurologist, Autonomic Unit, National Hospital for Neurology & Neurosurgery, Queen Square, London, United Kingdom
Familial dysautonomia (FD) is an inherited disorder of the nervous system that affects the development and survival of autonomic neurons. Typical cardiovascular autonomic symptoms are severe drop in blood pressure upon standing, without appropriate compensatory increases in heart rate, blood pressure lability, thermostatic dysregulation, hypoventilation, and recurrent autonomic crises episodes of producing severe high blood pressure. Some patients also experience faints (vasovagal syncope). Symptoms tend to be worse in the morning, in hot or humid weather, when the bladder is full, or before a large bowel movement. Symptoms due to hypotension become more prominent in the adult years and can limit function and mobility.

Recent Advances in the Treatment of Mitochondrial Ophthalmic Diseases
Dr. Umur A. Kayabasi, Lifemed Health Center, Uskudar University, Istanbul, Turkey
Chronic Progressive External Ophthalmoplegia (CPEO) and Leber's Hereditary Optic Neuropathy (LHON) are mitochondrial diseases which affect eye movements and the optic nerve. Until recently, there were no cures for both conditions. Genetic testing is necessary for the confirmation of the diagnosis. Gene therapy is the most promising treatment and clinical trials are being carried out at many centers. Other than gene therapy, some medications like Idebenone are being used in other clinical trials. All these advances give us hope that effective treatments will soon be available in both diseases.

B12 deficiency and Gestational diabetes – an update
Dr Vimal Karani S, University of Reading, Food & Nutritional Sciences, School of Chemistry Food & Pharmacy, Reading, United Kingdom
**Biochemical insights into Primary hyperoxaluria type III.**

Dr Kerry Loomes, School of Biological Sciences, University of Auckland, Auckland, New Zealand

Primary hyperoxaluria 3 (PH3) is a rare, autosomal-recessive inherited disorder characterized by increased oxalate production. It is caused by mutations in the HOGA1 gene encoding the enzyme 4-hydroxy-2-oxoglutarate aldolase (HOGA). Although these clinical mutations lead to the loss of enzymatic function it is still not clear what the metabolic fates of these mutant are within the cell. In this presentation I will describe our research showing the mechanisms by which the cell processes these aberrant HOGA forms as well as findings on another associated activity of HOGA that participates in the Kreb's cycle.

**Enzyme replacement therapy for lysosomal storage disorders: the pharmacology of marginal gains**

Dr Robin Lachmann, National Hospital for Neurology and Neurosurgery, London, United Kingdom

The first enzyme replacement therapy for Gaucher disease was introduced 25 years ago and has been a transformative treatment. Licensed ERTs for a further 7 LSDs are now available, but unfortunately none has so far approached the efficacy of ERT in Gaucher. I will discuss the reasons why these therapies have been therapeutically disappointing for patients and their physicians, yet financially highly successful for drug companies.

**Managing Familial Dysautonomia in a North London DGH: A paediatrician's steep learning curve**

Dr Su Laurent, Royal Free London NHS Foundation Trust, Barnet Hospital, Barnet, Hertfordshire, United Kingdom

**Alkaptonuria - Metabolic response to treatment with Nitisinone**

Dr Anna M Milan, Royal Liverpool and Broadgreen University Hospitals, Liverpool, United Kingdom

Alkaptonuria (AKU), rare inborn error of metabolism results in accumulation of homogentisic acid (HGA) in tissues and excretion in urine. HGA oxidises to benzoquinones which are responsible for the black appearance of urine and the destructive ochronotic pigment deposited in cartilage, bone and other connective tissues. Nitisinone is being used off-licence to treat AKU, at the National AKU centre in Liverpool, and as part of large scale clinical trials (DevelopAKUre consortium). Dose dependent reduction in urine HGA has been determined, with concurrent rise in serum tyrosine; no effect on serum or urine phenylalanine supports metabolic changes in the tyrosine pathway.

**Computational approaches to targeted drug design in metabolic diseases**

Dr Adina Milac, Department of Bioinformatics and Structural Biochemistry, Institute of Biochemistry of the Romanian Academy, Romania

Metabolic disorders are often associated with defects in specific enzymes, produced by inherited mutations. Although these mutations can be easily identified through fast high-throughput sequencing technology, understanding their functional consequences and deciphering the molecular mechanisms require detailed knowledge of 3D structure, dynamics and interactions with molecular partners. We will present in silico techniques that can be effectively used to elucidate the relationship between a protein sequence, 3D structure and its (mis)function, with emphasis on various drug design strategies.

**GRK2 as a new integrative node in obesity and insulin resistance: multi organ effects**

Dr Cristina Murga, Centro de Biología Molecular Severo Ochoa (CSIC-UAM), Madrid, Spain

Obesity is characterized by the abnormal accumulation of fat in an organism and poses a serious risk to health. An integrated view taking into account the precise contribution of different organs and signaling cascades is essential to combat obesity and insulin resistance. In this talk, I will summarize recent work from our laboratory, focusing on the study of the integrated response of the most important organs to the global pathophysiology of obesity and insulin resistance, with specific emphasis on the role of the G protein-coupled receptor kinase 2 (GRK2) signaling hub.
Respiratory Problems in Familial Dysautonomia
Professor Channa Maayan, Hadassah Medical Center, Kiryat Hadassah, Jerusalem, Israel
Abnormal development and progressive degeneration of the autonomic and sensory nervous systems in the Familial Dysautonomia (FD) causes functional impairment of most body systems. Pulmonary problems are important causes for increased morbidity and mortality. The main pulmonary problems are:
1. Aspirations: The defective coordination of the gastrointestinal system causes misdirection of food, saliva and fluids into the lung as well as gastroesophageal reflux. These leading to recurrent pneumonias, atelectasis, chronic interstitial and bronchiectatic lung disease, hypoxia, high CO2 and pulmonary hypertension. Choking can even be a cause of death.
2. Restrictive lung disease: Spinal curvature is seen in most FD patients especially at puberty. This will cause a decrease of lung volumes.
3. Control of breathing: Low CO2 sensitivity, abnormal O2 sensitivity, small lung volumes, high CO2 blood tension, alternating circulation delay as well as cardiac output and the fact that the hypoxia is coupled with hypotension causes risk of apnea, periodic breathing and respiratory arrest especially during sleep.
4. Breath holding spells (BHS): can last later than the usual 3 years, until 6-7 years. BHS can be triggered by stress, crying as well as laughter.
Better understanding of the respiratory problems in FD has led more appropriate and improved treatment as well as increased life expectancy.

Using Dried Blood Spot Testing in the management of Tyrosinaemia Type 1
Dr Roshni Vara, Evelina Children’s Hospital, St Thomas’ Hospital, London, UK
A lab harmonisation project to enable dry blood spot testing in the management of Tyrosinaemia Type 1

The impact of genomics on rare disease research
Dr Jonathan Milner, Deputy Chairman, Abcam plc, Cambridge, United Kingdom

Familial Dysautonomia: Genotype, Phenotype and Translational Research
Dr Lucy Norcliffe-Kaufmann, University School of Medicine, New York, United States
Familial dysautonomia (FD) is a rare neurological disorder caused by a splice mutation in the IKBKAP gene. The mutation arose within the small Jewish founder population in Eastern Europe in the 1500s and became prevalent during the period of rapid population expansion within the Pale of Settlement. The carrier rate is 1:32 in Jews descending from that region. The genotype results in a tissue-specific deficiency in IKAP, a protein involved in the development and survival of mostly afferent (sensory) neurons, which leads to widespread organ dysfunction and increased mortality. Lesions in the IXth and Xth cranial nerves result in afferent baroreflex failure, with stress-induced hypertension and orthostatic hypotension. With advances in clinical care, FD has changed from a once fatal pediatric disorder into a now chronic orphan disease. Neurodegenerative features of the disease include progressive optic atrophy and worsening gait ataxia. Despite this being a rare medically fragile population, controlled clinical trials have been conducted. Search for better treatments as well as a neuro-protective agent is ongoing.

Neurometabolic Disorders in Children
Dr. Germaine Pierre, UHBT, Education Centre, Bristol, United Kingdom
There are an increasing number of neurometabolic disorders in childhood. Diagnosis can be challenging especially when patients present with nonspecific problems. A practical approach to investigation and diagnosis is needed. Disorders with therapeutic options should be prioritised.

The role of Open Innovation in development of new therapies for rare diseases
Dr Martino Picardo, Stevenage Bioscience Catalyst, Stevenage, Herts, United Kingdom
The role of Open Innovation in the pre-competitive R&D space for development of new drugs is growing, alongside more traditional methods of strategic alliance and collaboration leading to better models for new drugs. In this case, the author will describe how an open Innovation ecosystem is
being developed at the GSK R&D site in Stevenage. More specifically, we will discuss how the very specific challenges relating to developing new drugs for rare diseases is being tackled using new case studies.

**Professor Shamima Rahman**, UCL Institute of Child Health, London, United Kingdom

Since the first discovery of mitochondrial DNA mutations almost 30 years ago, genetic diagnosis of mitochondrial disease has posed enormous challenges, because of the extreme clinical, biochemical and genetic diversity of these disorders. In recent years next generation sequencing approaches have allowed a paradigm shift in the diagnostic approach to mitochondrial disease, moving away from the traditional methods of muscle biopsy followed by enzymology and Sanger sequencing of candidate genes. This presentation reveals the results of whole exome sequencing of a single centre cohort of 100 patients with suspected mitochondrial disease, including 4 patient subgroups: 1) isolated deficiency of respiratory chain complex I; 2) isolated complex IV deficiency; 3) multiple respiratory chain defects; and 4) patients with a strong clinical suspicion of mitochondrial disease despite normal respiratory chain enzymology.

**Next Generation Sequencing (NGS) approach to discovery of rare neuro-metabolic disorders**
Dr Maja Tarailo-Graovac, Centre for Molecular Medicine and Therapeutics, Vancouver, Canada

Next generation sequencing (NGS) has an unprecedented impact on discovery and diagnosis of rare disorders. In our Omics2TreatID program, we combine the deep metabolic phenotyping with whole exome/genome sequencing (WES/WGS) to accelerate discovery of treatable neuro-metabolic diseases. We developed and applied a semi-automated gene-discovery bioinformatics pipeline, which involves manual inspection of data quality and collaborative interactions between clinicians and bioinformaticians to identify causal variants. We have performed WES in more than 150 and WGS in more than 30 consecutively enrolled patients with intellectual developmental disorders (IDD) and unexplained metabolic phenotypes, and will present on impact of our approach.

**DevelopAKUre: a patient-led clinical trial for a rare disease**
Mr Oliver Timmis, AKU Society, Cambridge, United Kingdom

DevelopAKUre is a series of phase II and phase III clinical trials, assessing a new drug, nitisinone, as a potential treatment for the ultra-rare disease AKU. The AKU Society is a patient group, and a leading partner in the trials, contributing patient identification, recruitment, retention and general patient support. We believe that involving a patient group as a key partner in rare disease research is essential to provide excellent patient care especially where the patient population is small.

**Circulating microRNAs as markers of the liver neoplastic process in a mouse model of hereditary tyrosinemia**
Professor Robert M. Tanguay, Dept. Biologie moléculaire, Biochimie médicale & pathologie, Medical School, Université Laval, Québec, Canada

Hereditary tyrosinemia type 1 (HT1) is a severe inborn error of metabolism, impacting the tyrosine catabolic pathway with a high incidence of hepatocellular carcinoma (HCC). Using a HT1 murine model, we investigated the changes in circulating miRNAs associated with the liver neoplastic process. Plasma miRNAs profiles were found to be good non-invasive markers of the state of the liver and were detected earlier that AFP in the oncogenic process. Assessment of validated miRNAs in HT1 patients designate these molecules as potential biomarkers for monitoring HT1 damage progression, improving diagnosis for early HCC detection and the design of novel therapeutic targets.

**Steroid profiling for rare diseases**
Dr Bruno Vogt, Inselspital, University Hospital of Bern, Bern, Switzerland

Steroid disturbances are part of the rare metabolic diseases. Steroid profiling in urine and plasma allows to detect such rare diseases illustrated in a patient with a very rare metabolic disease.
Treatable Neurometabolic Diseases in the 21st Century
Dr. Clara van Karnebeek, University of British Columbia, Vancouver, Canada
Neurometabolic disorders present with heterogeneous phenotypes, including developmental delay, intellectual disability, cognitive decline, epilepsy, movement disorders, psychiatric disease, etc. Diagnosis is challenging yet essential to allow for timely initiation of therapy to avoid brain damage (diet, medication, stem cell transplant). Implementation of our TIDE biochemical diagnostic algorithm identified treatable conditions in more than 5% of 500 children with intellectual disability. We present our novel approach integrating metabolomics and genomics for the discovery of 11 new neurometabolic diseases and diagnoses impacting on management in 40% of 50 unexplained neurometabolic patients studied, permitting causal therapies to improve outcomes.

Biliary transporter mutations; implications for gestational liver disease
Professor Catherine Williamson, King's College London, London, United Kingdom
The biliary transporters ABCB11, ABCB4 and APT8B1 contribute to transport of bile acids and phospholipids at the hepatic canalicular membrane. Mutations have been reported in each of these genes in various forms of hereditary cholestasis, including intrahepatic cholestasis of pregnancy, a relatively common form of cholestasis that occurs in pregnancy where it results in gestational elevation of maternal and fetal serum bile acids. This in turn is associated with an increased risk of adverse pregnancy outcomes, including preterm labour and stillbirth. Gestational cholestasis can result from the interaction between elevated levels of reproductive hormones in genetically susceptible women.

Day 1:

Oral Presentation Abstracts
Oral presentations will be added after the submission deadline

Day 2:

Oral Presentation Abstracts

THE USE OF PHENOMICS IN THE DIAGNOSIS, TREATMENT AND POTENTIAL TREATMENT OF LAMINOPATHIES
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Phenomics is an emerging transdiscipline dedicated to the systematic study of the physical and biochemical traits of organisms — as they change in response to genetic mutation and environmental influences.

Laminopathies and other nuclear envelopapathies have a large variety of clinical symptoms including skeletal and cardiac muscular dystrophy, lipodystrophy and diabetes, dysplasia, dermo- or neuropathy, leukodystrophy, and premature aging. Often symptoms develop after birth, typically during childhood or adolescence. Some laminopathies cause early death, and mutations of lamin B (LMNB1 gene) may be lethal before or at birth. It is known that there is a significant inherited
component to the disease with patients with classical laminopathy having an identified mutations in the LMNA gene.

The nuclear envelopathy with the highest frequency in human populations is Emery-Dreifuss muscular dystrophy caused by an X-linked mutation affecting an estimated 1 in 100,000 people.

The situations in which genetic predisposition to Laminopathy can become manifest or subject to interventions will be explored.

Day 3:

**Oral Presentation Abstracts**

Oral presentations will be added after the submission deadline

**CHOLIC ACID THERAPY IN ZELLWEGER SPECTRUM DISORDERS**


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Introduction: Zellweger spectrum disorders (ZSDs) are characterized by a failure in peroxisome formation, caused by autosomal recessive mutations in different PEX genes. At least some of the progressive and irreversible clinical abnormalities in patients with a ZSD, particularly liver dysfunction, are caused by the accumulation of toxic bile acid intermediates. We investigated whether cholic acid supplementation can suppress bile acid synthesis, reduce accumulation of toxic bile acid intermediates and improve liver function in these patients.

Methods: An open label, pretest-posttest design study was conducted including 19 patients with a ZSD. Participants were followed longitudinally during a period of 2.5 years prior to the start of the intervention. Subsequently, all patients received oral cholic acid and were followed during nine months of treatment. Bile acids, peroxisomal metabolites, liver function and liver stiffness were measured at baseline and 4, 12 and 36 weeks after start of cholic acid treatment.

Results: During cholic acid treatment, bile acid synthesis decreased in the majority of patients. Reduced levels of bile acid intermediates (dihydroxycholestanoic acid [DHCA] and trihydroxycholestanoic acid [THCA]) were found in plasma and excretion of bile acid intermediates in urine was diminished. In patients with advanced liver disease (n=4), cholic acid treatment resulted in increased levels of plasma transaminases, bilirubin and cholic acid with only a minor reduction in bile acid intermediates.

Conclusions: Oral cholic acid therapy can be used in the majority of patients with a ZSD, leading to at least partial suppression of bile acid synthesis. However, caution is needed in patients with advanced liver disease due to possible hepatotoxic effects. A prolonged treatment period is needed to investigate whether cholic acid treatment can alter clinical outcome.
**Poster Presentation Abstracts**

Poster abstracts will be finalised weeks before the event

**CYSTINOSIS: ALGERIAN EXPERIENCE**


**Introduction:** Cystinosis is a hereditary disease characterized by lysosomal accumulation of cystine in various organs; renal disease is manifested by proximal tubular dysfunction with progressive renal failure. This work aims to describe clinical, biological, therapeutic and evolutionary aspects of cystinosis treated with cysteamine in a Division of General Pediatrics in Algiers.

**Materials and Methods:** Retrospective study of records of children with cystinosis over nine years, between January 1, 2006 and December 31, 2015.

**Results:** 11 records were collected and used. The sex ratio is 4.5 with a clear male predominance. The circumstances of discovery are dominated by polydipsia and growth retardation. The diagnosis is evoked given the signs of proximal tubular damage in 7 of 11 patients, held given the eye disease in 6 of 11 patients. The average age of diagnosis is 31.4 months. Measurement of intra-leukocyte cystine is performed in 10 of 11 patients; mean age of treatment is 37 months.

**Discussion**
- Despite the autosomal recessive disease, there was a clear male predominance (sex ratio: 4.5 vs 1.3 in Gahl study (1) and 1.1 in Brodin-Sartarius study (2)).
- The rate of family inbreeding estimated at 77% in our study vs 14% in Brodin-Sartarius study (2), explains the high rate of family history (77 %).
- The delay in diagnosis (3 years vs 1.3 years in Bertholet-Thomas study (3)) and in care is related to the absence of means of biological diagnostic (set up in the department in 2012 in association with ORPHAN EUROPE).
- The high rate of intra leukocyte cystine during treatment (5.6 mol vs 2.5 mol as target value (1)) is related to the problem of supplying a specific treatment.
- No patient received growth hormone, whence the advantage of the treatment of Fanconi syndrome and the nasogastric or gastrostomy feeding (4).

**CONCLUSION:**
- Cystinosis exists in our population, especially given that a high rate of inbreeding is shown.
- The evocation of the diagnosis is easy when we stop to think about it: tubular syndrome (8/9), vitamin rickets resistant (7/9), corneal deposits (5/9)
- The diagnosis requires a special logistics (isolation of leukocytes, assessing intra-leukocyte cystine), which is not always available.
- The main objective being to delay kidney failure, the regular supply of drugs is a prerequisite to achieve this goal.

Infant cystinosis, as many orphan diseases is facing many difficulties in the diagnosis and management of patients. Its prognosis is related to the improvement of means of diagnosis and, accordingly, early management.

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β - CYCLODEXTRIN POLYROTAXANES AS POTENTIAL NIEMANN-PICK TYPE C THERAPEUTICS: FROM DESIGN TO IN VIVO THERAPEUTIC EFFICACY

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Niemann-Pick Type C disease (NPC) is a rare metabolic disorder characterized by aberrant accumulation of cholesterol within the late endosome/lysosome. Ranges of visceral and neurological symptoms present clinically- including a progressive neurodegeneration. NPC is ultimately fatal and there are no FDA approved treatments currently available to patients.

2-hydroxypropyl-β-cyclodextrin (HP-β-CD), a small molecule glucose macrocycle, has been shown to be an effective NPC therapeutic, with administration increasing the average lifetime of NPC mice by as much as 50% and delaying neurodegeneration. Although promising, HP-β-CD treatment has significant shortcomings, including poor bioavailability and pharmacokinetic profile- limiting potential efficacy. To address these issues, we sought to design high molecular weight, HP-β-CD pro-drug delivery vehicles, known as polyrotaxanes (PR). These non-covalent rod-shaped assemblies are intended to prevent rapid renal excretion, increase CD residence time within the body, and improve the overall pharmacokinetics and bioavailability of each injected dose.

A family of PR materials has been generated using a variety of CD derivatives and triblock co-polymer cores resulting in vastly differing overall physiochemical properties. In vitro, PR localize to the late endosome/lysosome of NPC cells and mobilize cholesterol from sites of sequestration more effectively, on a molar basis, than treatment with HP-β-CD. [1,2] In vivo, PR pharmacokinetic profile, toxicity, and therapeutic efficacy are affected by the structure and dynamics of their rod-like morphologies. We show that highly threaded PR circulate for up to 24 hours and deposit in the liver, whereas lung deposition and rapid clearance is observed for PR with lower threading percentages. In contrast, physiochemical differences have little influence on toxicity.[3]

In NPC mice, PR administration effectively diminishes sequestered cholesterol within the visceral organs at molar concentrations 10-to-100-fold lower than HP-β-CD. PR architectures featuring increased threading and high polymer core hydrophobicity appear to generate enhanced therapeutic efficacy. Presented herein is the full course of PR development as potential NPC treatment- from design to therapeutic efficacy in vivo. In all, PR scaffolds hold great promise for clinical translation as potential treatments for NPC patients.