# Conquer Chiari
# Research Conference
## 2012

# Conquer Chiari
# Research Conference 2012

**November 8th & 9th**

Building on the success of past conferences, this two-day professional research conference will focus on new developments in Chiari research, discuss issues in diagnosis and treatment, and foster collaborations. The event brings together the top physicians and researchers involved with Chiari Malformation in a format designed to maximize the exchange of ideas.

## Organizers:


Rick Labuda, Executive Director
**Conquer Chiari**
director@conquerchiari.org
724-940-0116

Konstantin Slavin, MD
**University of Illinois-Chicago**
kslavin@uic.edu
312-996-4842

Francis Loth, PhD
**University of Akron**
loth@uakron.edu
330-972-6820


## Location:

Hyatt Regency O'Hare
Chicago, Illinois
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## Sponsors:

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Column of Hope
Chiari & Syringomyelia Research Foundation

# Thursday - November 8th, 2012

| Time | Speaker | Topic |
|---|---|---|
| 7:30 | *Registration & Continental Breakfast* | |
| 7:55 | **Rick Labuda -** Conquer Chiari | *Welcome & Goal Setting* |
| 8:00 | **Mark Luciano -** Cleveland Clinic | *Chiari push or pull: anatomical correlations in health and disease* |
| 8:30 | **Georgy Koentges -** University of Warwick | *Cellular and Molecular Processes Affecting Posterior Fossa Volume* |
| 9:00 | **Marcus Stoodley -** Macquarie University | *Syrinx Formation* |
| 9:30 | **Scott Parker -** Vanderbilt University | *Accurately Measuring Outcomes After Surgery for Adult Chiari I Malformation:* |
| 10:00 | *Break & Informal Discussion* | |
| 10:15 | **John Oro -** Chiari Treatment Center | *Brain Motion & Intraoperative Ultrasonography in the Chiari I Malformation* |
| 10:45 | **Spyros Sgouros -** University of Athens and "Mitera" Childrens Hospital, Athens, Greece | *Evolution of Pseudomeningocele Following Cranio-Vertebral Decompression Without Duraplasty in Children With Chiari I Malformation* |
| 11:15 | **David Frim -** University of Chicago | *Chicago Chiari Outcome Scale: Predicting outcome Based on Presentation* |
| 11:45 | *Morning Discussion* | |
| 12:00 | **Lunch** | |
| 1:00 | **Jorge Lazareff -** UCLA | *Transoperative SSEP: What we Decompress When we Decompress the Posterior Fossa* |
| 1:30 | **David Sandberg -** University of Texas | *Outcomes in Pediatric Chiari Patients followed without Surgery* |
| 2:00 | **Cormac Maher -** University of Michigan | *The Distribution of Cerebellar Tonsil Position: Implications for Understanding the Chiari Malformation* |
| 2:30 | *Break & Informal Discussion* | |
| 2:45 | **Thomas Moriarty -** Norton Neuroscience | *Surgical Treatment of Chiari: Morbidity and Recurrence* |
| 3:15 | **Harold Rekate -** The Chiari Institute | *The Odontoid Process and Chiari 1 Malformation* |
| 3:45 | **Maureen Lacy -** University of Chicago | *Cognitive Interventions in Pediatric CM* |
| 4:15 | **John Tew -** Mayfield Clinic<br>**Konstantin Slavin -** UIC | *Moderated Discussion* |
| 5:00 | *Break* | |
| 6:30 | **Dinner: Bermans Iskandar -** University of Wisconsin Sponsored by Column of Hope | *Keynote: CNS Regeneration* |

# Friday - November 9th, 2012

| Time | Speaker | Topic |
|---|---|---|
| 7:30 | *Continental Breakfast* | |
| 8:00 | **Dr. John Heiss -** National Institutes of Health | *Quality of Life in Syringomyelia with/without Chiari* |
| 8:30 | **Dr. Enver Bogdanov -** Kazan State Medical University (Russia) | *Epidemiology of Syringomyelia* |
| 9:00 | **Dr. Georgy Koentges -** University of Warwick | *Establishing New Classification System for Illnesses All Leading to Chiari I* |
| 9:30 | **Dr. Simon Gregory -** Duke University | *Identification of Pediatric Chiari Type I Malformation Subtypes Using Clinical and Biological Factors* |
| 10:00 | *Break & Informal Discussion* | |
| 10:15 | **Dr. Rafeeque Bhadelia -** Harvard University | *Physiology-based Quantitative Assessment of CSF Flow Obstruction at the Foramen Magnum in Patients with Chiari I Malformation* |
| 10:45 | **Dr. Rajiv Bapuraj** - University of Michigan | *Dynamic MRI and Quantitative MRI CSF Flow Studies in Chiari I Malformations* |
| 11:15 | **Dr. Francis Loth -** University of Akron | *Spinal Canal Hydrodynamics of Chiari Patients: Importance of Geometry* |
| 11:45 | *Morning Discussion* | |
| 12:00 | **Lunch** | |
| 1:00 | **Dr. Bryn Martin -** University of Akron | *4D MRI Applied to the Investigation of Chiari & Syringomyelia* |
| 1:30 | **Dr. Mark Quigley** | *CSF Flow in Normal Adult and Pediatric Subjects: CSF Flow Abnormalities as a Diagnostic in Chiari I Patients* |
| 2:00 | **Rick Labuda - Conquer Chiari** | *Conquer Chiari Patient Database - A Tool for Chiari Researchers* |
| 2:15 | **Mark Kane - Column of Hope** | *Column of Hope Research Programs* |
| 2:30 | *Break & Informal Discussion* | |
| 2:45 - 4:00 | **Dr. John Tew -** Mayfield Clinic<br>**Dr. Konstantin Slavin -** UIC | *Moderated Discussion* |

**Dr. Mark Luciano**
*Cleveland Clinic*

## Chiari Push or Pull: Anatomical Correlations in Health and Disease

The etiology of Chiari Malformation remains unclear and is likely multifactorial and varied. Tonsil herniation may be due to the "push" of a small posterior fossa and/or hydrodynamic forces. Much more controversial is the concept of "pull" evoking by the concept of a tethered cord etiology.

This preliminary anatomical study seeks to investigate the relationship between brainstem and cerebellar position and the level of the spinal cord terminus in three populations:

1) Chiari I patients presenting for evaluation (N= 53)

2) Tethered cord patients (N= 43)

3) Normal patients who underwent cranial and spinal MR imaging for other reasons and were negative for mass lesions or anatomical abnormality (N= 50)

Measurements of brainstem position, tonsil descent, posterior fossa midsagittal area and conus position were taken from MRI's retrospectively and analyzed through group comparison and correlation.

The spinal cord position in the "normal' and Chiari patients were not significantly different. The average posterior fossa size of the Chiari patients was significantly smaller than in the "normal" patients, but interestingly was even smaller in the tethered group. There was a significant correlation between spinal cord position and cervicomedular measurements in the normal patient group but not in the Chiari group. While these findings do support normal and pathological relationships between the cranial and spinal anatomy, they do not support the concept of a tether etiology in Chiari I malformation.

## Biography

Mark G. Luciano, MD, PhD, FACS, came to the Cleveland Clinic Department of Neurosurgery in 1993 after training in general neurosurgery at the University of Pennsylvania and in pediatric neurosurgery at Harvard's Boston Children's Hospital. In addition, he was trained in research through a PhD from Tulane University and a fellowship at the National Institutes of Health. At Cleveland Clinic, he also holds adjunct positions in neuroscience research and in biomedical engineering.

Dr. Luciano is board-certified in general neurosurgery and in pediatric neurosurgery. He is Head of Congenital and Pediatric Neurosurgery and Co-Director of the Pediatric Neurology Center at Cleveland Clinic. His patients are children and adults with neurological congenital anomalies, hydrocephalus, cerebral cysts, tumors, craniofacial anomalies, tethered cord, Chiari malformation and cerebral palsy. As part of his section, Dr. Luciano also directs the Neuroendoscopy and CSF Disorders program. He is known nationally and internationally for his clinical activity, research and educational work in neuroendoscopy, a form of minimally invasive neurosurgery. Children and adults are referred who are in need of endoscopic procedures, such as those with ventricular tumors and cysts. Dr. Luciano has directed Cleveland-area, national and international courses in neuroendoscopy and has developed new techniques in minimally invasive neurosurgery.

**Prof Georgy Koentges**
*University of Warwick*

## 1. Cellular and Molecular Processes Affecting Posterior Fossa Volume
## 2. Establishing New Classification System for Illnesses All Leading to Chiari I

In the past I have reported on the role of neural crest in forming a much wider spectrum of structures in the cranial base than previously thought. I will describe the cellular processes involved in shaping the postcranial fossa at different times of development. This is of interest as the genes involved in these steps are likely to be disease candidates for future human genetic studies. Problems in these processes can now explain mechanistic links between changes in basicranial structure, suboccipital headaches and other problems affecting Chiari patients. They can also explain the biphasic distribution of affected patients. Most recently we have, supported by Conquer Chiari, started to focus on later aspects of growth that affect the topology of the postcranial fossa and discovered unexpected invasive processes at work that appear to change again the fate map of the postnatal skull, particularly in the cranial base and cervical region. I will report on these first preliminary findings and their biomedical implications.

Insights into the genetics of Chiari I involve various aspects of retinoid signaling and Hox gene mediated patterning. These have testable implications for neurologists. In a second talk I will outline our current concepts on the etiology of Chiari I in the framework of a new disease classification with each category having different testable criteria, testable through high-resolution imaging and genetics. I am keen to interact as widely as possible with clinicians on this conference – in the hope that we will be able a) to query patients according to this new disease classification, b) with the expectation to radically extend the scope of treatment opportunities for surgeons and neurologists, cognizant of the concept that Chiari I is the outcome of several different diseases and syndromes, each of which requiring a different therapeutic approach.

Please feel free to contact me at g.koentges@warwick.ac.uk.

## Biography

Professor Georgy Koentges of the Warwick University School of Life Sciences has been studying craniofacial development since the 90s. He was trained as a comparative anatomist and embryologist in Tuebingen and London, worked on the so-called neural crest cells that form the craniofacial skeleton with Prof Lumsden FRS and discovered fundamental rules of how the right muscles get connected to different parts of the skeleton.

After 3.5yrs at Harvard, where he worked with Prof Dulac and Nobel Prize winner Prof Richard Axel on developing mice in which neuronal circuitry can be labeled genetically he established his laboratory at UCL, London, refocusing on the role of neural crest in organizing the head and shoulder region.

He developed novel techniques to genetically mark and manipulate the embryonic cells that make up the complex neck and shoulder region, which culminated in work that was published in Nature in 2005. In this work he discovered a rather unusual origin of the cranial base and the postcranial fossa region and shed entirely new light onto the aetiology of Chiari and a host of other craniofacial/skeletal illnesses.

He has been funded by the Wellcome Trust, MRC and Conquer Chiari, a US charity solely dedicated to Chiari work, in successive grant rounds. With the help of Conquer Chiari he continues to study the fundamental molecular and cellular mechanism that cause this debilitating disease, trying to understand how meninges, skeletal defects and sub-occipital headaches are linked at a deeper mechanistic level. Only such genetic understanding will enable us to predict such illness better - on the basis of our genetic make-up - and open up new avenues of treating it that are more effective than present.

He will be delighted to interact with all participants as fully as possible on this exciting meeting.

**Dr. Marcus Stoodley**
*Macquarie University*

## Syrinx Formation

**Purpose**: Syringomyelia is a condition where expanding cysts form in the spinal cord in association with spinal cord injury, cranio-vertebral junction abnormalities, arachnoiditis, and spinal tumours. These cysts may cause spinal cord damage, resulting in pain, sensory loss, paralysis, or even death. The origin of syringomyelia fluid is one of the greatest enigmas in neuroscience. Often considered to simply contain CSF, syringomyelia pathophysiology is more complex because syrinx pressure must exceed CSF pressure for syrinx expansion to occur. Treatment of syringomyelia is unsatisfactory and improved treatment is unlikely to be developed without a greater understanding of syrinx pathogenesis.

**Methods**: A series of experiments has been conducted using rodent and ovine models of syringomyelia. These experiments have examined CSF flow in the subarachnoid space and spinal cord, and the cellular and molecular conditions in the cord tissue around syrinx cavities. In addition, computational modelling has been used to explore CSF dynamics and the effects of perturbations of CSF flow in the subarachnoid space. MRI was used to study CSF flow in patients with syringomyelia and cranio-cervical junction abnormalities.

**Results**: A normal flow of CSF from the subarachnoid space to the spinal cord central canal was demonstrated. This flow is mainly via the perivascular spaces. Pulsations in the subarachnoid space are necessary for this flow to occur. Obstruction of CSF flow in the subarachnoid space increases local subarachnoid pulse pressure and may increase flow in the perivascular spaces. In addition, the timing of pulse transmission through the subarachnoid space may have a crucial effect on perivascular flow. In animal models of syringomyelia the perivascular flow continues, even when there is evidence of raised syrinx pressure. The blood-spinal cord barrier remains structurally and functionally disrupted around syrinx cavities, with evidence of fluid flow from vessels in the cord in to the cord substance. There is an increase in aquaporin-4 channel and a decrease in potassium channel expression in astrocytes around syrinx cavities. Fluid flows out of syrinx cavities in to the surrounding extracellular space with a preferential flow in to the central grey matter and central canal.

**Conclusion**: Advances have been made in the understanding of CSF physiology in the subarachnoid space and spinal cord and in the pathogenesis of syringomyelia. These advances are impacting surgical decision-making. There is a possibility that further advances will result in pharmacological treatments for this disabling condition.

## Biography

Professor Stoodley graduated with honours from medical school at the University of Queensland. After completing neurosurgery training in Australia, he completed further subspecialty training in vascular neurosurgery at Stanford University and the University of Chicago. Professor Stoodley has clinical expertise in neurovascular surgery and a special interest in Chiari malformation and syringomyelia. He directs the neurosurgery laboratory at the Australian School of Advanced Medicine and continues research on syringomyelia as well as developing new biological treatments for brain arteriovenous malformations (AVMs). He has produced more than 100 publications and has supervised over 15 research students.

**Dr. Scott Parker**
*Vanderbilt University*

## Accurately Measuring Outcomes After Surgery for Adult Chiari I Malformation: Determining the Most Valid and Responsive Instruments

**Background:** Over the last few decades, there has been a transition to utilizing patient-centered tools to assess surgical effectiveness. Many different validated patient-reported outcome instruments (PROi) are available to assess surgical effectiveness for various disease states. However, none of these instruments have been validated for outcomes of adult Chiari I Malformation. We set out to determine the relative validity and responsiveness of various PROi in measuring outcomes after surgery for adult Chiari I Malformation.

**Methods:** Fifty patients undergoing suboccipital craniotomy for adult Chiari I Malformation were followed for one year. Baseline and 1-year patient-reported outcomes [VAS-Head, VAS-Neck, Neck Disability Index (NDI), Headache Disability Index (HDI), SF-12 PCS, SF-12 MCS, Zung Depression and EQ-5D] were assessed. Patients were also asked whether they felt their health condition was improved by surgery (meaningful effectiveness). Primary objective was to assess 1) the accuracy of VAS-Head, VAS-Neck, NDI and HDI to discriminate between meaningful effectiveness versus non-meaningful effective improvements in pain and disability, and 2) the validity of SF-12, Zung depression scale, and EQ5D to discriminate between meaningful effectiveness versus non-meaningful effective improvements in general health and quality of life (QOL). Receiver operating characteristic (ROC) curves were generated for each outcomes instrument. Area under the curves (AUC) >0.80 was considered an accurate discriminator. The difference between standardized response means (SRM) in patients reporting meaningful improvement versus not were calculated to determine the relative responsiveness of each outcomes instrument to changes in pain and QOL after surgery.

**Results:** For pain and disability, NDI had the highest AUC = 0.90, suggesting it as the most accurate discriminator and valid measure of meaningful effectiveness. VAS-Head (AUC=0.74), HDI (AUC=0.72) and VAS-Neck (AUC=0.68) were less accurate. NDI was also the most responsive to post-operative improvement (SRM difference: 1.87), followed by VAS-Head (SRM difference: 1.32), VAS-Neck (SRM difference: 0.70) and HDI (SRM difference: 0.67). For general health and quality of life, SF-12 PCS (AUC: 0.93), EQ-5D (AUC: 0.87) and Zung (AUC: 0.83) were all accurate discriminators and valid measures of meaningful effectiveness. SF-12 MCS (AUC: 0.76) was a less accurate discriminator. SF-12 PCS was also most responsive (SRM difference: 2.17), followed by EQ-5D (SRM difference: 1.63), Zung (SRM difference: 1.27) and SF-12 MCS (SRM difference: 1.00).

**Conclusions:** For pain and disability, Neck Disability Index is the most valid and responsive measure of effectiveness after surgery for Chiari I Malformation. For health-related quality of life, SF-12 PCS and EQ-5D are the most valid and responsive measures of effectiveness after surgery for Chiari I Malformation. Neck Disability Index with SF-12 or EQ-5D is the most valid measure of pain and disability, and quality of life in patients with Chiari I Malformation and should be utilized in comparative effectiveness outcomes studies.

## Biography

Scott L. Parker is currently a neurosurgery resident at Vanderbilt University Medical Center. His research interests include neurosurgical clinical outcomes, particularly comparative effectiveness and cost-utility analyses.

**Dr. John Oro**
*Chiari Treatment Center*

## Brain Motion & Intraoperative Ultrasonography in the Chiari I Malformation

Intracranial arterial and capillary expansion that occurs in the brain during systole results in centripetal and caudal movement of the brain in the supratentorial compartment and anterior and caudal movement in the posterior fossa. The resulting transient remolding of the brain creates a piston-like action that affects the cerebellar tonsils. In the Chiari I malformation, cyclic pistoning of impacted tonsils (occurring at a maximum speed of 1.5 mm/sec in healthy subjects), can deform the tonsils and result in fibrosis or blistering of the tonsillar tips, creation of a cervico-medullary kink, and progressive elongation and compression of the medulla. The dynamics and anatomy of this process as visualized on intraoperative ultrasonography and intraoperative imaging, as well as improvement in MRI cervico-medullary anatomy following posterior fossa decompression, will be reviewed.

## Biography

Dr. Oró's commitment to advancing Chiari care developed during his tenure as Professor and Chief of Neurosurgery at the University of Missouri. He recalls that, "In 1998, I developed a special interest in Chiari I Malformation because I saw that many people were not receiving adequate evaluation and treatment." Since his initial interest, Dr. Oró's dedication to providing the best surgical procedures and patient care has increased. In 2005, he relocated to Colorado to continue his practice in neurosurgery.

As the Medical Director of Neurosciences at The Medical Center of Aurora, Dr. Oró's expertise covers a variety of neurological disorders, including brain tumors, cerebral aneurysms and disorders of the spine. His unique dedication to aiding those afflicted with Chiari I Malformation has made him one of the most sought after surgeons in the nation.

Dr. Oró has been listed among the Best Doctors in America since 2001, and he has been listed among America's Top Surgeons since 2007. Beyond being a highly skilled surgeon, he has held numerous appointments, serving on boards and committees at the state and national levels.

**Dr. Spyros Sgouros**
*University of Athens and "Mitera" Childrens Hospital, Athens, Greece*

## Evolution of Pseudomeningocele Following Cranio-Vertebral Decompression Without Duraplasty in Children With Chiari I Malformation

**Introduction:** It was noticed that many children who had cranio-vertebral decompression for Chiari I without duraplasty, at 12 months postoperatively the surgically created pseudomeningocele had substantially decreased in size, in comparison to immediately postoperatively. Serial MR scans were analysed to establish the natural evolution of pseudomeningocele.

**Material and Methods:** MR scans of children with isolated Chiari I malformation obtained preoperatively, early postoperatively and at 12 months or later postoperatively were analysed. Mid-sagittal images were graded for the size of the pseudomeningocele at the cranio-vertebral junction. The pseudomeningocele was graded as non-existent, small (equal to the normal cisterna magna), moderate (bigger than the normal cisterna magna but not exceeding the borders of the craniectomy), large (beyond the limits of the craniectomy) and very large (within the cervical muscles). Signs of arachnoid adhesions at the cranio-vertebral junction were recorded. Only patients who had one cranio-vertebral decompression and did not require any further re-exploration were included. Patients with other syndromes (eg. craniosynostosis) or with secondary hindbrain hernia (eg. previously shunted) were excluded. The operation was considered failure if the syringomyelia did not improve radiologically or if there were persisting symptoms (eg pain). The success of the operation was correlated with the size of the pseudomeningocele and the presence of adhesions using chi-square.

**Results:** A total of 37 children were included. Mean age at diagnosis was 121 months (range: 7.5-192 months). In 4 patients (10.8%) the craniovertebral decompression was considered unsuccessful, in 3 due to persistent syringomyelia and in 1 due to persistent headaches. At the early postoperative scan the pseudomeningocele was large in 27 and very large in 10. At the late postoperative scan the pseudomeningocele was non-existent in 3, small in 4, moderate in 7, large in 16 an very large in 7. In 8 patients there were arachnoid adhesions at the operation site in the late scan. There was a correlation between the presence of adhesions and the small size of the pseudomeningocele ($p=.002$, chi-square). There was a correlation between the presence of adhesions and the failure of the operation ($p=.026$, chi-square) and the small size of the pseudomeningocele and the failure of the operation ($p=.041$, chi-square). Of the 7 patients who had very large pseudomeningocele in the late scans, 2 had mild ventriculomegaly and 3 had signs of intracranial hypertension preoperatively.

**Conclusion:** In children who had cranio-vertebral decompression for Chiari I malformation with the technique of pseudomeningocele (without duraplasty), as the healing proceeds, in a significant proportion (30%) the pseudomeningocele reduces in size significantly, almost down to normal cisterna magna. Those who have persistent very large pseudomeningoceles may harbour intracranial hypertension. The development of postoperative adhesions is associated with failure of the operation.

## Biography

Prof. S. Sgouros is the Head of the Department of Pediatric Neurosurgery at “Mitera” Childrens Hospital, Athens, Greece. He is also Assistant Professor of Neurosurgery at the Medical School of the University of Athens.

He studied Medicine at the University of Athens (1979-1985). He trained in Surgery and Neurosurgery in Britain (1988-1998). He subspecialised in Pediatric Neurosurgery and Craniofacial Surgery. He trained also in Paris, France (1996) and Hannover, Germany (1997).

He is Fellow of the Royal College of Physicians and Surgeons of Glasgow (1992), Fellow of the Intercollegiate Board of Surgical Neurology (1997) and Doctor of Medicine at the University of Birmingham (2000).

He worked as Consultant Neurosurgeon at the Birmingham Children’s Hospital and the Queen Elizabeth Hospital, Birmingham, Britain and as Senior Lecturer in Neurosurgery at the University of Birmingham (1998-2007). He returned to Greece in 2007 and worked initially at “Attikon” University Hospital in Athens (2007-2010) and subsequently at “Mitera” Childrens Hospital.

He specialises in all aspects of Pediatric Neurosurgery such as surgery for brain and spinal cord tumours, neuroendoscopy, craniofacial surgery, surgery for syringomyelia, congenital and CSF disorders and spasticity.

**Dr. David Frim**
*University of Chicago*

## Chicago Chiari Outcome Scale: Predicting outcome based on presentation

In response to a need to predict and compare Chiari outcomes based on symptoms or treatments, the Chicago Chiari Outcome Scale (CCOS) was designed to rate outcome after Chiari decompression in four areas on a 16-point scale: pain symptoms, non-pain symptoms, function, and surgical complications. This approach has since been internally validated and subsequently used to correlate surgical outcome with presenting Chiari symptoms. In this presentation, the structure of the CCOS in comparison to previous Chiari outcome systems will be reviewed and critiqued. Retrospective application of the CCOS to an institutional database, which yielded several significant correlations of outcome to pre-operative symptoms, will be presented. Possible uses of the CCOS in the Chiari community will lead to the description of several potential outcome questions that could be answered by prospective application of the CCOS to large series of operative Chiari patients.

## Biography

Dr. Frim, Professor of Surgery and Pediatrics Chief, Section of Neurosurgery, has performed hundreds of complex neurosurgical procedures on infants and children. He also provides neurosurgical care for adults, particularly for individuals who have congenital diseases. Dr. Frim has developed expertise in a variety of minimally invasive, stereotactic, and neuro-endoscopic techniques to approach complex lesions of the brain and spine. He has particular interests and significant experience in surgical procedures to treat hydrocephalus, congenital anomalies of the nervous system such as Chiari malformation, epilepsy, myelodysplasia, brain and spine tumors, and trauma.

In addition to his clinical work, Dr. Frim is an active medical researcher and educator. His current investigations include studies of the neuroprotective effects of surfactant poloxamer molecules, investigations of the cognitive outcomes in hydrocephalus and Chiari patients, and development of treatment strategies for congenital complex anomalies of the nervous system.

**Dr. Jorge Lazareff**
*UCLA*

## What We Decompress When We Decompress The Posterior Fossa

A great deal of uncertainty exists regarding the Chiari type I malformation. Its pathophysiology is poorly understood, its natural history is unpredictable, and its response to various treatment methods has not been supported with robust evidence. This uncertainty manifests itself in myriad ways, but the most pressing issue for surgeons is the practice variation of the management of Chiari type I malformations.

A common objective in the great majority of surgeries for Chiari type I is to achieve some degree of decompression of the posterior fossa, “to enlarge the narrowed space occupied by the brain stem, cerebellum and spinal cord” (Russell and Dondal 1935). Different lengths, depths and widths of craniectomy/laminectomy have been proposed. In some occasions the authors support their rationale with intuitive statements such as “facilitate circulation of fluid in the leptomeningeal space”, or to “liberate the tonsils” (Penfield and Coburn 1938) In 17 papers published between 1935 and 2008 the common objective of the surgical procedure was to restore the subarachnoid flow of CSF.

Certainly everybody engaged in treating patients with Chiari malformation is searching for an objective way of determining the length and the extent of the posterior fossa decompression. The ideal method is one that can be used intraoperative to guide management and in recent times there have been reports of the usefulness of somatosensory evoked potentials (SSEP) and brainstem auditory evoked responses (BAER) in patients with Chiari type I (Anderson RCE et al 2003, Zamel K et al. 2008). In these studies the authors have observed an improving of these values after the removal of the bone. Nonetheless the extent of the craniectomy has never clearly defined by the authors who performed intraoperative SSEP. And it is well known that in some cases when the craniectomy is very extensive the cerebellar tissue may slump into the craniectomy site and the cervical canal.

It is our practice to perform craniectomy of a defined size bounded superiorly by the nuchal line. We also have been replacing the bone flap in a fashion that does not defeat the purpose of achieving a decompression of the posterior fossa. Other authors have also reported similar procedures. In order to increase our understanding of the effect of bone decompression over the cerebellum we decided to test with SSEP and BAER during our regulated craniectomy. As our practice is to replace the bone flap we also wanted to establish if such a procedure altered the neurophysiological measurements.

Thirteen consecutive patients underwent sub occipital decompression for treatment of symptomatic Chiari I. Craniectomy was restricted to the inferior aspect of the nuchal line, and in most cases the bone flap was replaced. Neuronal conduction was monitored continuously with median nerve somatosensory evoked potentials (M-SEP), posterior tibial nerve somatosensory evoked potentials (T-SEP), BAER, or a combination. The M-SEP N20, T-SEP P37, and BAER V latencies were recorded at four milestones – preoperatively, following craniotomy, following durotomy, and following closure.

**Results:** Five males and eight females, with average age of 9 years, were studied. Clinical improvement was noted in all 13 patients. M-SEP N20 latency decreased from a mean of 18.55 at baseline to 17.75 ms after craniotomy ($p = 0.01$); to 17.06 ms after durotomy ($p = 0.01$); and to 16.68 ms after closing ($p = 0.02$). T-SEP P37 latency did not change significantly. BAER V latency decreased from a mean of 6.25 ms at baseline to 6.14 ms after craniotomy ($p = 0.04$); to 5.98 ms after durotomy ($p = 0.01$); and to 5.95 ms after closing ($p = 0.45$).

Together these findings suggest that our approximately 3 cm x 4 cm craniectomy restricted to the nuchal line can achieve a similar extent of decompression as a more extensive one, implying that sufficient space can be created with a less drastic approach. Our series also demonstrates improvements in M-SEPs and BAERs following both craniectomy and duroplasty, suggesting that in those instances duroplasty indeed had a decompressive effect. This finding could potentially explain the superior symptomatic improvements seen with duroplasty in the literature. Duroplasty is effective for effective in smaller craniectomies, while it may be superfluous with a larger craniectomy. It is not our intention to advocate for a specific method, but to share with our colleagues our findings.

## Biography

Dr. Lazareff is a Professor and Director of the Pediatric Neurosurgery Program. His primary focus is the treatment of children with neurosurgical disorders. He is also involved with the UCLA Global Neuro Health Program.

**Dr. David Sandberg**
*University of Texas*

## Outcomes in Pediatric Chiari I Patients Followed Without Surgery

**Object:** We reviewed outcomes for pediatric patients with Chiari I Malformations (CM-1) who were followed without surgical intervention in order to better define natural history.

**Methods:** We retrospectively reviewed 124 patients with CM-1 who presented between July, 1999 and July, 2008 and were managed without surgery. Patients ranged in age from 0.9 to 19.8 years (mean 7 years). Follow-up ranged from 1.0 to 8.6 years (mean 2.83 years). Imaging findings, symptoms, and neurological examinations were noted at presentation and for the duration of follow-up.

**Results:** Mean tonsillar herniation at presentation was 8.35 mm (range 5 to 22 mm). Seven patients had a syrinx at presentation. Syrinx size did not change in any of these patients on follow-up imaging studies. No new syrinxes developed in the remaining patients who underwent subsequent imaging. Of the 81 patients who obtained initial imaging studies because of symptoms, 67 demonstrated symptoms that were not typical of CM-1. Of the 14 patients with symptoms attributed to CM-1, 9 had symptoms that were not severe or frequent enough to warrant surgery, and surgery was recommended in the remaining 5 patients but the parents declined surgery. CM-1 was also diagnosed in 43 asymptomatic patients who had imaging studies performed for various reasons. No new neurological deficits were noted in any patient for the duration of follow-up.

**Conclusions:** The majority of patients with CM-1 followed conservatively do not progress clinically or radiographically. Longer follow-up will be required to determine if symptoms or new neurological findings develop over the course of many years.

## Biography

David I. Sandberg, MD, FAANS, FACS, FAAP is Director of Pediatric Neurosurgery and Associate Professor at the University of Texas Health Science Center at Houston and an attending neurosurgeon at Children's Memorial Hermann Hospital and the University of Texas MD Anderson Cancer Center.

He received his undergraduate degree from Harvard University, his medical degree from the Johns Hopkins University School of Medicine, and completed neurosurgery residency training at Weill Medical College of Cornell University/New York Presbyterian Hospital.

Dr. Sandberg was awarded the Resident Traveling Fellowship in Pediatric Neurosurgery by the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS), and he completed this fellowship at the Hospital for Sick Children in Toronto, Canada.

After residency, he completed fellowship training in pediatric neurosurgery at the Children's Hospital Los Angeles, which is affiliated with the Keck School of Medicine of the University of Southern California.

He then joined the faculty at the University of Miami Miller School of Medicine and Miami Children's Hospital, where he stayed for nearly eight years before moving to Houston for his current position.

He is a diplomate of the American Board of Neurological Surgery and the American Board of Pediatric Neurological Surgery and has co-authored numerous manuscripts and textbooks in peer-reviewed journals on a variety of topics in pediatric neurosurgery.

**Dr. Cormac Maher**
*University of Michigan*

## The Distribution of Cerebellar Tonsil Position: Implications for Understanding the Chiari Malformation

**Background:** Prior attempts to define normal cerebellar tonsillar position have been limited by small numbers of subjects that have precluded analysis of normal distribution by age group. Our objective is to analyze cerebellar tonsillar position in every age range.

**Methods:** 2400 subjects were randomly selected and organized into 8 age groups from a database of 62,533 consecutive subjects undergoing imaging. MRIs were directly examined for tonsil location, morphology and other features. Those with a history or imaging finding of posterior fossa abnormalities not related to CM were excluded. Measurements of caudal extent of the cerebellar tonsils were made at mid-sagittal and the lowest parasagittal position.

**Results:** The mean tonsillar height decreased slightly with advancing age in childhood and increased with advancing age in the adult age range. Increasing age in the adult age range was associated with a decreased likelihood of tonsil position 5mm or more below the foramen magnum (p=0.0004) . In general, the distribution of lowest tonsil position in each age group followed a normal distribution. Patients with pegged morphology were more likely to have tonsillar location at least 5mm below the foramen magnum (85%), compared with those with intermediate (38%) and rounded (1.7%) morphology (p<0.0001). Female sex was associated with lower mean tonsil position (p<0.0001).An increasing tendency for asymmetric tonsil position, especially with a lower right tonsil, was noted with lower tonsil position (p<0.0001).

**Conclusions:** Cerebellar tonsil position follows an essentially normal distribution and varies significantly by age. This finding has implications for advancing our understanding of the CM.

**Figure 1:**
Mean lowest tonsil position by age in 2400 subjects

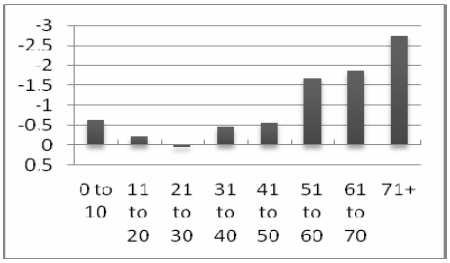
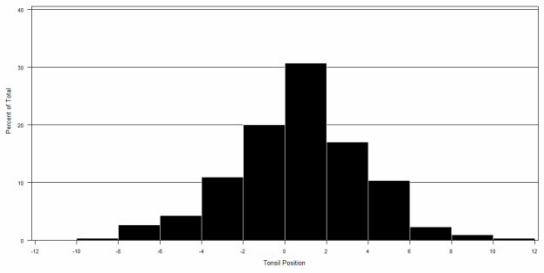



**Figure 2:**
Tonsillar distribution, Ages 21-30




## Biography

Cormac O. Maher, M.D. is a neurosurgeon specializing in the surgical treatment of children. Dr. Maher's major areas of clinical interest include the surgical treatment of arteriovenous malformations, moyamoya disease, cavernous malformations, pediatric brain tumors, congenital malformations including cysts and Chiari malformation, spinal dysraphism, and hydrocephalus.

Dr. Maher is a graduate of Georgetown University, where he obtained a Doctorate of Medicine and was elected to the Alpha Omega Alpha Medical Honor Society. He completed his surgical internship and neurosurgical residency at the Mayo Clinic in Rochester, Minnesota. After completion of his neurosurgical residency training at Mayo, Dr. Maher moved to Boston, Massachusetts for dedicated training in Pediatric Neurosurgery under the direction of R. Michael Scott, M.D. of Harvard University and Boston Children's Hospital.

Dr. Maher is an active clinician-investigator and has made over 100 presentations of his work at national medical meetings. His work has appeared in many medical journals including the Journal of Neurosurgery, Stroke, Neurosurgery, and Neurology.

**Dr. Thomas Moriarty**
*Norton Neuroscience*

## Surgical Treatment of Chiari: Morbidity and Recurrence

**Introduction:** The optimal surgical management of Chiari malformations has not been defined. Evidence continues to accrue that supports decompression without duraplasty as an effective treatment to achieve symptomatic relief and anatomical decompression. The risks and benefits of this less invasive operation need to be compared to decompression with duraplasty.

**Methods:** A retrospective review was performed of all Chiari decompressions from 2001 to 2012 by a single surgeon at a single institution. Data was analyzed for outcome, morbidity, recurrence and syrinx resolution. Anatomical and radiographic predictors of recurrence were investigated.

**Results:** 243 consecutive chiari operations (223 unique patients) were reviewed. Patients were between the age of 1-19 (avg. 6.6) and 53 % female. Follow up ranged from 6 months to 11 years. 123 received posterior fossa decompressions without duraplasty (PFD) and 120 patients received posterior fossa decompressions with duraplasty (PFDD). 100 patients presented with a chiari and syrinx. 26 were treated with PFD for unique reasons, 74 were treated with PFDD. Of the 123 PFD patients, 14 (11%) underwent a subsequent PFDD for symptomatic recurrence; three did not significantly improve with the second procedure. Of the 120 patients receiving a PFDD, 4 (3%) needed a repeat procedure for symptomatic recurrence. PFDD patients had longer OR times and longer hospital stays for procedure related symptoms. The time to recurrence ranged from 5 months to almost 10 years (PFD (n=15): average 23 months (range 5-66) vs. PFDD (n=3): average 65 months (range 52-116).

**Conclusions:** While PFD patients had a higher rate of recurrent symptoms requiring redo-decompression, this may be justified by a significantly lower morbidity for 89 -90% of patients. The time to recurrence for PFDD is significantly longer and may be an under recognized complication of PFDD. An understanding of the tradeoff between morbidity and recurrence should be included in the informed consent for Chiari surgery.

## Biography

Dr. Moriarty was born in New York and earned a BS degree from SUNY Buffalo in Science and Literature. He completed the Mount Sinai School of Medicine MD-PhD program in 1991 with a PhD focus on molecular neurobiology. He attended the Harvard Medical School Neurosurgery Training Program at the Brigham and Women's Hospital and Boston Children's Hospital. His research focus in Boston was intra-operative imaging and computer assisted neurosurgery. His clinical focus was pediatric neurosurgery.

He moved to the University of Louisville in 1997 and assumed the role of Chief of Pediatric Neurosurgery at the Kosair Children's Hospital in 1998. Since then the program has more than tripled in volume and expanded abilities particularly in congenital anomalies, cancer care, epilepsy and trauma. In 2009 the program became part of the Norton Neuroscience Institute, an organization with which currently has more than 50 neurosurgeons, neurologists, physiatrist and oncologists focused on adult and pediatric neurosciences.

**Dr. Harold Rekate**
*The Chiari Institute*

## The Odontoid Process and Chiari 1 Malformation

The fact that herniation of the cerebellar tonsils is called the Chiari I malformation leads to the assumption that it is a distinct, clearly defined entity. Nothing could be farther from the truth. A better name would be “hindbrain herniation” a term frequently used in the UK. As such there are many pathophysiologic mechanisms that lead to this condition. At this point the actual primary cause of this condition can be determined in a minority of patients with the Chiari I malformation.

One cause that is often ignored relates to the crowding of the foramen magnum by encroachment of the posterior fossa structures by compression from the odontoid process anterior to the brainstem. The presentation discussed here relates to the diagnosis and treatment of hindbrain herniation due to anterior distortion of the foramen magnum by the odontoid process. There is no consensus as to the radiographic classification and description of the relationships when the odontoid process comes lie within the foramen magnum, distorting the brainstem and leading to chronic tonsilar herniation. The diagnosis of “basilar invagination” or “cranial settling” has been based on the relationships of the odontoid process with the skull base as seen on plain Xrays or tomograms. The use of MRI to analyze these conditions has made the measurements made on plain radiographs outdated. Sagittal T2 images show clearly the relationships of the odontoid to the brainstem and cerebellar tonsils directly.

Grabb and his colleagues at the University of Alabama have shown the importance of the position of the odontoid process and developed a technique to quantify this relationship. The measurements involve a line drawn from bottom of the clivus to the posterior –inferior base of the odontoid and drawing a line perpendicular to this line to the apex of the odontoid process as it relates to the brainstem. The resulting Grabb-Oakes line should be less than 9 mm. When this measurement is greater than or equal to 9 mm it is assumed that the craniovertebral junction is unstable and probably the cause of the hindbrain hernia. Even though the vector of movement of the odontoid is posterior rather than the more easily recognized superior displacement it is reasonable to see this abnormality as a form of “basilar invagination.” This condition can either be congenital and associated with a retroflexed odontoid process and short clivus or may be due to a ligamentous laxity in conditions such as Ehlers-Danlos syndrome.

Generally these patients are diagnosed with Chiari I malformation but the role of the odontoid is ignored. This is particularly important as this relationship is dependent on the position of the head in the scanner. Posterior fossa decompression without occipitocervical fusion is likely to make the condition worse since it disrupts the posterior tension band and with time further compression occurs. The management of this condition relates to extradural boney decompression and intraoperative reduction of the craniovertebral junction in Extension and distraction and fusion of the occiput to C3. Patients from 8 months to 54 years have successfully undergone the procedure with low risk and excellent results in long term follow-up.

## Biography

Harold Rekate is the Director of The Chiari Institute and Professor of Neurosurgery at Hofstra Northshore LIJ College of Medicine.

He received his medical training from the Medical College of Virginia, Richmond, VA, and completed his Residency in neurosurgery at University Hospitals of Cleveland (Case Western Reserve University). He received his undergraduate education at BS, Duke University, Durham, NC.

Dr. Rekate is a former Chairman of the Joint Section on Pediatric Neurological Surgery of the American Association of Neurologic Surgeons and Congress of Neurologic Surgeons. He is also past president of both the International Society of Neurologic Surgery and the American Society of Neurologic Surgeons.

He specializes in Chiari Malformations types 1 and 2, Congenital Neurosurgical Conditions Regardless of Age, Hypothalamic Hamartoma, Hydrocephalus, Pseudotumor Cerebri, Spina Bifida and Surgical Management of Epilepsy. He is the author of over 200 articles and book chapters and editor of two books on neurosurgical topics.

**Dr. Maureen Lacy**
*University of Chicago*

## Cognitive Interventions in Pediatric CM

The neurocognitive functioning of children with Chiari Malformation Type I has received scant attention in the literature in the past. In our pilot study, funded by the Conquer Chiari Foundation, children with CMI completed a comprehensive battery of standardized and widely utilized tests designed to elucidate common cognitive strengths and weaknesses. Testing revealed a high percentage of children displayed working memory and attention deficits.

In the next phase of the study, we designed an intervention study targeting these cognitive domains. Children displaying cognitive impairment by objective exam and/or parental report were enrolled in the trial. Children were assigned to one of 3 treatment based aims:

a) Weekly individual one on one therapist designed cognitive rehabilitation sessions

b) Online participation in a computerized program designed to target working memory and processing speed skills
c) A commercially available and popular online game.

As the trial is ongoing, initial results will be presented along with recommendations for clinicians and future studies.

## Biography

Maureen Lacy, PhD, is an Associate Professor in the department of Psychiatry and Behavioral Neurosciences at The University of Chicago Medical Center. Dr. Lacy's current clinical and research endeavors include identifying a neurocognitive profile associated with Chiari Malformation Type I and then developing targeted interventions and remediation strategies for patients and families.

## Dr. Bermans Iskandar

*University of Wisconsin*

### CNS Regeneration

The effect of folate on CNS repair remains superior to any other experimental intervention published in the interval, and is the first example of the role of epigenetics in CNS repair. Conquer Chiari felt it would be interesting, if not useful, to this group if Dr. Iskandar were to present his work in light of our current understanding of CNS injury and repair, as this fits in perfectly within the research mission of the organization.

### Biography

Dr. Iskandar is Professor of Neurosurgery and Pediatrics, and Director of the Pediatric Neurosurgery program at the University of Wisconsin Hospital and Clinics. His areas of clinical expertise include Chiari malformation and syringomyelia, brachial plexus reconstruction, and endoscopic surgery for tumors and congenital brain anomalies. He gained national recognition for novel imaging techniques aimed at minimizing the radiation exposure of children with hydrocephalus, as well as developing new technology to analyze the craniocervical CSF flow in children with Chiari malformation and Syringomyelia. Dr. Iskandar has committed a large portion of his time to run a basic laboratory research, in which he studies ways to repair the central nervous system (brain and spinal cord) after injury. This has significant impact on patients with Chiari and syringomyelia who suffer from motor and sensory dysfunction as well as pain related to injury to the brain and spinal cord. In his studies, Dr. Iskandar's group has uncovered a crucial link between the folate and B12 pathway, epigenetics, and CNS repair, which has gained national and international recognition, leading to invited presentations at prominent venues in the U.S., Crete, and Italy, and funding from the National Institutes of Health.

**Dr. John Heiss**
*National Institutes of Health*

## Quality of Life in Syringomyelia with/without Chiari

**Introduction:** Syringomyelia typically presents with sensory loss, pain, and/or weakness. Progressive symptoms prompt surgery, which usually reduces syrinx size and halts neurological deterioration. The effect of reducing syrinx diameter on quality of life and pain level is uncertain, requiring further study.

**Methods:** An ongoing prospective longitudinal study has enrolled 18 adults with primary spinal syringomyelia, 7 with Chiari I malformation (CMI)-associated syringomyelia, and 6 with CMI without syringomyelia. Average pain (NRS, numeric rating scale), Karnofsky performance score (KPS), and MRI-measured maximal syrinx diameter were evaluated initially, after 3 months, and then annually. Follow-up was 3-24 (7±4; μ±SD) months. Patients with progressive neurologic signs from primary spinal syringomyelia (8), CMI-syringomyelia (5), and CMI (3) alone underwent surgery. Patients with stable symptoms were observed. Pain level and functional ability (ΔKPS) were compared between the operative and non-operative groups.

**Results:** At last follow-up, pain was reduced more in surgical (-0.6±1.7) than non-surgical patients (+0.2±2.2, p=0.04; unpaired t-test). In addition, pain reduction occurred more frequently in surgical patients (10/16) than non-surgical patients (4/15; p=0.04, Chi-Square). KPS improved in surgical (μ=75 pre; 82 post; p=0.03) and non-surgical (73 initial, 78 final; p=0.05) patients to a similar degree (p=0.74). Syrinx diameter correlated insignificantly with pain (surgical, $R^2$=0.05, p=0.18; non-surgical, $R^2$=0.0004, p=0.33).

**Conclusions:** All patients with syringomyelia and/or CMI had pain and most had reduced quality of life. Syringomyelia pain persisted over time and responded incompletely to surgical treatment, presumably because surgery cannot reverse the central spinal cord injury that results from syringomyelia.

## Biography

Source: www.asap.org

John D. Heiss, M.D. is the Head of the Clinical Unit of the Surgical Neurology Branch, National Institute of Neurological Diseases and Stroke (NINDS), National Institutes of Health (NIH), in Bethesda, Maryland.

Shortly after Dr. Heiss came to the National Institutes of Health in 1991, he and his mentor, Dr. Edward Oldfield, designed a clinical study to better understand the mechanism involved in the development of syringomyelia in patients with Chiari I malformation. This study resulted in a series of papers that helped to explain the process. He subsequently developed research protocols to study syringomyelia not associated with the Chiari I malformation and to study the genetics of Chiari I malformation.

Dr. Heiss joined the Institutional Review Board (IRB) of the NINDS in 1998 and became Vice-Chairman in 2002. In 2007, Dr. Heiss became Head of the Clinical Unit of the Surgical Neurology Branch. He also has the rank of Clinical Professor of Neurosurgery at George Washington University Medical School.

**Dr. Enver Bogdanov**
*Kazan State Medical University (Russia)*

## Epidemiology of Syringomyelia

Syringomyelia is a polyetiologic disorder characterized by abnormal fluid-filled cavities within the spinal cord. Most cases of syringomyelia are associated with Chiari malformation. The mean prevalence of MRI-confirmed syringomyelia ranges, in different countries, between 2 and 13 per 100,000 inhabitants. But there are clear ethnic and geographic differences in rates of syringomyelia and some associated conditions. However, the extent to which these differences are due to environmental factors versus genetic factors remains unknown. Epidemiological investigations are very important for distinct estimation the problem of syringomyelia.

The Republic of Tatarstan in Russia – a region with a known high prevalence of syringomyelia. However, these epidemiological data were obtained in the period before the introduction of MRI. We have studied the prevalence of MRI-verified observations syringomyelia associated with Chiari malformation in the adult population of the Republic of Tatarstan. The study involved the observation identified in the period from 1998 to 2007, patients with severe trauma, space-occupying lesions of the brain or spinal cord is not included in this study.

Total was found 866 patients with Chiari malformation (men – 52%). Syringomyelia was detected in 42% of patients. Chiari malformation mean prevalence was 30 per 100,000 adult population, syringomyelia - 12.6. Familial forms of the disease were observed in 5%. Our own data, there are difference in the prevalence of syringomyelia between the Tatars and other groups, at 15 and 9 per 100,000 inhabitants, respectively. In addition, the prevalence among both Tatars and other ethnic groups varied significantly across different regions of Tatarstan, ranging between 3.7 and 93 per 100,000 adults in Tartars and between 2 and 92 per 100,000 in a population composed mainly of Russians. We were found a predominance of Chiari malformation and syringomyelia in the northern regions of the Tatarstan. The high prevalence of syringomyelia in the North of Tatarstan may be associated not just with the predominance of the Tatar population in this region but also the employment of these people, mainly in physically demanding jobs in agriculture (author's own data). Interestingly, however, syringomyelia prevalence may also vary with the soil type.

In addition, clinically "asymptomatic" Chiari malformation was detected in 12% of patients with MRI verified multifocal demyelinating lesions of the brain, 5% of patients with ischemic stroke and 19% of patients with transient ischemic attack admitted to a stroke unit.

The study may help to improve the understanding and treatment of Chiari malformation and syringomyelia.

**Dr. Simon Gregory**
*Duke University*

## Identification of Pediatric Chiari Type I Malformation Subtypes Using Clinical and Biological Factors

Chiari type I malformation (CMI) is part of a pathological continuum of hindbrain malformations clinically defined as an inferior displacement of the cerebellar tonsils below the foramen magnum. Although many individuals with Chiari are classified as having CMI, it is clear that a lot of variation exists in terms of the pattern and severity of symptoms, response to therapy, presence of associated conditions, age of disease onset, and the extent of tonsillar herniation. This variation is poorly understood and a more objective, sensitive method is needed in order to identify more homogeneous groups of patients, which may not be readily observed by more traditional phenotyping methods. In order to address this issue, we ascertained a collection of pediatric CMI patients through the Pediatric Neurosurgery Department at Duke University Medical Center. Individuals were enrolled in the study if they were diagnosed with CMI and underwent posterior fossa (PF) decompression surgery with duraplasty (performed by H.F. or G.G). Individuals were excluded from the study if the patient had a 1) supratentorial or infratentorial tumor, 2) lumbar shunt, 3) significant history of birth trauma, 4) history of any cervical or cranial surgery, or 5) history of myelomeningocele. Blood samples and a small piece of dura mater (< 5mm x 5mm) obtained during surgery were collected from each patient for the analysis of whole genome expression. In addition, patients were asked to complete a detailed clinical questionnaire and sign a medical release for pre-surgical MRIs. Under the supervision of a board certified neuroradiologist (D.E), a series of 16 measurements and 8 area estimates were made using sagittal T1-weighted, pre-surgical MRIs.

In total, 70 patients were enrolled in this study over a period of 20 months. RNA was extracted from both dura and blood samples using Qiagen's RNeasy fibrous tissue mini kits and Paxgene blood RNA kits, respectively. 88 blood and dura RNA samples along with eight RNA controls were run on Illumina HumanHT-12 v4.0 beadchips in order to generate genome-wide expression profiles. After data quality assessment, all samples remained for subsequent analysis. Out of the 44 patients, 36 questionnaires and 40 pre-surgical MRIs for measurements were collected, leaving 32 total patients with all available biological and clinical data for analysis.

Clinical and biological information was used both separately and jointly to identify more homogeneous classes, or subtypes in a collection of 32 patients. When analyzed separately, consistency with respect to the sets of subtypes would suggest a biological importance of the subtypes identified using clinical factors alone. However, we suspect that biological features, such as gene expression patterns, are necessary to identify biologically relevant subtypes which may not be readily observed using clinical features alone. Either result provides important information regarding future identification and classification of CMI patients. In addition, important information regarding the biology of the disorder was also obtained by identifying the underlying genes/regulatory pathways which may be driving the heterogeneity. Results of ongoing analyses will be presented at the research conference in November.

## Biography

Dr. Gregory is an Associate Professor in the Section of Medical Genetics, Department of Medicine. Dr. Gregory's role in the Duke CHG is to apply the experience gained from leading the mapping of the mouse genome and sequencing human chromosome 1 to elucidating the molecular mechanisms underlying multi-factorial diseases. His primary area of research involves the identific ation of the complex genetic factors that give rise to the development of cardiovascular disease and the detection of genes involved in multiple sclerosis. Dr. Gregory's group is also pioneering the application of high-resolution genomic microarrays for the discovery of chromosomal abnormalities and identification of epigenetic factors associated with human diseases such as cancer and autism. This project aims to correlate copy number profiles and factors such as methylation, with clinical phenotypes and differential levels of gene expression. His areas of special expertise are genome mapping, positional cloning and determining the effect that sequence variation has upon the etiology of genetic disease. Dr. Gregory is also director of the Duke Bioinformatics Workshop, a forum for researchers to gain in-depth experience of using publicly available molecular genomics databases.

Dr. Gregory is a member of the graduate faculty of the Computational Biology and Bioinformatics, Molecular Genetics and Microbiology and University Program in Genetics and Genomics programs.

**Dr. Rafeeque Bhadelia**
*Harvard University*

## Physiology-based Quantitative Assessment of CSF Flow Obstruction at the Foramen Magnum in Patients with Chiari I Malformation

**Purpose:** Invasive pressure studies have shown that physiological challenges such as the Valsalva maneuver or coughing produce transient changes in intracranial and intraspinal pressures, and may be responsible for producing headache and syringomyelia in patients with Chiari I malformation. In this preliminary study, our purpose was to quantify CSF flow in response to a Valsalva maneuver in normal subjects using ultrafast MRI.

**Methods:** Routine cine phase contrast (cine-PC) was modified using a combination of parallel imaging, half-Fourier and multiple phase encodes per heart beat to achieve a fast cine-PC sequence with ≤15s acquisition time. CSF flow in 8 healthy subjects was then assessed just below the foramen magnum at rest, during, and immediately after a controlled Valsalva maneuver. CSF mean displacement volume ( $\overline{V}_{CSF}$ ) during the cardiac cycle and CSF flow waveform peak to peak amplitude ( $A_{pp}$ ) were determined. Using pencil-beam imaging (PBI) with temporal resolution ≤60 milliseconds, two subjects were scanned for 90-seconds during which resting, Valsalva and post-Valsalva CSF flow were measured. Respiration and heart rate were also recorded simultaneously.

**Results:** During Valsalva, $\overline{V}_{CSF}$ decreased from 0.56 ± 0.24 ml to 0.37 ± 0.17 ml ($p<0.001$) and $A_{pp}$ decreased from 4.51 ± 1.6 ml/s to 3.52 ± 1.6 ml/s ($p<0.007$). Immediately after Valsalva, $\overline{V}_{CSF}$ (0.69 ± 0.19 ml) and $A_{pp}$ (5.28 ± 1.5 ml/s) increased significantly compared to both resting and Valsalva values. PBI showed similar findings but Valsalva induced transient changes in CSF flow, heart rate and respiration were better depicted with PBI due to its real-time capability.

**Conclusion:** The dynamic CSF flow response to physiological challenge can be quantified using both fast cine-PC and PBI. Our observations suggest that PBI is a potentially superior method for measuring altered Valsalva response in Chiari I malformation patients.

## Biography

Dr. Bhadelia is Clinical Director of Neuroradiology at the Beth Israel Deaconess Medical Center in Boston. He is Associated Professor of Radiology at Tufts University School of Medicine and Lecturer in Radiology at Harvard Medical School. His research has focused on two main subjects: (1) Use of motion sensitive MRI techniques to image CSF flow pulsations in the head and spine, and (2) Use of MRI in community-based cohorts to study the effect of risk factors on the structure and function on the aging brain. Dr. Bhadelia is currently working on developing a simple, quantitative, noninvasive MRI method to differentiate between Chiari I malformation patients who can and who cannot benefit from decompressive surgery.

**Dr. Rajiv Bapuraj**
*University of Michigan*

## Dynamic MRI and Quantitative MRI CSF Flow Studies in Chiari I Malformations

Quantification of cerebrospinal fluid (CSF) velocity within the foramen magnum subarachnoid space may be useful for selecting symptomatic candidates for Chiari decompression surgery. We evaluate the influence of different neck positions on craniovertebral junction (CVJ) and Sylvian aqueduct CSF velocities in both normal volunteers and patients with Chiari malformation type I (CMI).

Twenty two volunteers were prospectively evaluated with phase-contrast MRI scans performed perpendicular to the CVJ and the cerebral aqueduct. Ten symptomatic CMI patients were also scanned both preoperatively and at 12 months postoperatively. Each subject was scanned with the neck in the flexed, neutral, and extended positions. During the cardiac cycle, CSF amplitude of mean velocity (AMV) and amplitude of peak velocity (APV) were calculated at the CVJ and within the aqueduct for the 3 neck positions.

CSF velocities in the CVJ and within the aqueduct were significantly greater in CMI patients than in volunteers. In normal volunteers, both AMV and APV differed with respect to head position in both the cerebral aqueduct and anterior CVJ space. For preoperative CMI patients, AMV and APV differed between neutral and flexed neck positions and AMV differed between neutral and extended neck positions. For postoperative CMI patients, no differences were observed within the aqueduct or at the CVJ for any of the 3 neck positions.

Differences in aqueductal APV and AMV between normal volunteers and preoperative CMI patients in the neutral and neck flexion positions were identified. Between normal volunteers and postoperative CMI patients, differences in APV within the anterior CVJ space were identified in both the flexed and extended positions. Velocities were significantly greater in preoperative CMI patients than in normal volunteers at the CVJ and within the aqueduct. Velocities at the CVJ did not normalize following surgery in the CMI patients. Velocities in the aqueduct were significantly higher in preoperative CMI patients than in normal volunteers, but showed significant decrease following surgery with return to normal in both APV and AMV.

Neck position therefore does affect CSF velocities at the CVJ and within the cerebral aqueduct in normal healthy volunteers and symptomatic CMI patients. CSF velocities in the cerebral aqueduct are elevated preoperatively in CMI patients and normalized following surgery.

## Biography

Dr. Bapuraj is an Assistant Professor of Neuroradiology at the University of Michigan, specializing in Neuroradiology and Diagnostic Radiology. He received his medical training from Pt. B.D. Sharma Postgraduate Institute of Medical Sciences, where he also completed his residency, focusing on Radio-Diagnosis. After his residency, he completed fellowship training in Neuroadiology at All India Institute of Medical Sciences.

Selected Chiari related publications:

[1] Jennifer Strahle; Karin M Muraszko; Joseph Kapurch; J Rajiv Bapuraj; Hugh J L Garton; Cormac O Maher
Chiari malformation Type I and syrinx in children undergoing magnetic resonance imaging.
*Journal of Neurosurgery*. Pediatrics 2011;8(2):205-13.

[2] Jennifer Strahle; Karin M Muraszko; Joseph Kapurch; J Rajiv Bapuraj; Hugh J L Garton; Cormac O Maher
Natural history of Chiari malformation Type I following decision for conservative treatment.
*Journal of Neurosurgery*. Pediatrics 2011;8(2):214-21.

**Dr. Francis Loth**
*University of Akron*

## Spinal Canal Hydrodynamics of Chiari Patients: Importance of Geometry

**Introduction:** Type I Chiari malformation (CMI) is typically defined by herniation of the cerebellar tonsils 3-5 mm past the foramen magnum and neurological symptoms. However, studies have shown that some CMI patients with deep herniations can present with mild symptoms and vice versa. A number of studies have measured cerebrospinal fluid (CSF) velocity near the foramen magnum as an additional factor to explain CMI severity. These studies have also yielded mixed results. We hypothesized that quantification of CSF flow obstruction in terms of geometric and impedance parameters assessed near the foramen magnum would help objectively stratify CMI patients in terms of neurological symptom severity and from normal volunteers.

**Methods:** Twenty CMI patients were imaged pre-surgery at three different hospitals and classified as either symptomatic (severe neurological symptoms, recommended for surgery) or asymptomatic (mild neurological symptoms, not recommended for surgery). Symptomatic patients evaluated at two of the hospitals were also imaged post-surgery. A group of ten healthy control measurements were also obtained. High-resolution anatomy images were used to reconstruct 3D geometric models of the subarachnoid space from the foramen magnum to C2. The models were analyzed in two ways: 1) geometrically for distribution of hydraulic radius and cross-sectional area and 2) using CFD simulations to calculate LI over the first 2.5 cm of the model. To obtain a characteristic LI value for each case, LI was integrated from 1 to 8Hz giving the impedance to unsteady flow. The LI calculation was shown to be independent of the flow waveform shape. Thus, a generic CSF flow waveform was used for cases where subject-specific flow data was not available. Differences between groups for each parameter measured were compared statistically using a standard two-tail analysis of variance. In a similar manner, parameters were compared pre- and post-surgery for patients with both image sets.

**Results:** Average LI was found to be highest in symptomatic CMI patients, lower in asymptomatic CMI patients, and lowest in volunteers. Similarly, average values of mean hydraulic radius and mean cross-sectional area were found to be smallest in symptomatic CMI patients, larger in asymptomatic CMI patients, and largest in volunteers. Post-hoc statistical analysis revealed that both mean LI and mean hydraulic radius were significantly different between each of the three subject groupings. LI was found to have a strong linear correlation with the inverse of both mean hydraulic radius and mean cross-sectional area. However, certain cases did not follow this trend. Preliminary results comparing symptomatic CMI patients pre-surgery and post-surgery yielded mixed results. LI decreased by ~10% post-surgery in two patients, remained similar in another patient, and increased by ~20% in another patient.

**Conclusions:** LI, hydraulic radius, and cross-sectional area have utility in identifying geometric differences in the spinal SAS geometries of mildly and severely symptomatic CMI patients and normal volunteers. However, the clinical utility has yet to be determined and a greater number of pre- and post-surgical measurements are needed.

## Biography

Francis Loth, Ph.D. is an Associate Professor, F. Theodore Harrington Chair, and the Executive Director of the Chiari Research Center at the University of Akron. He holds a dual appointment in the Departments of Mechanical and Biomedical Engineering at the University of Akron. His research interests are in cardiovascular hemodynamics and biofluid mechanics of craniospinal disorders.

**Dr. Bryn Martin**
*University of Akron*

## Comparison of 4D phase-contrast MRI flow measurements to computational fluid dynamics simulations of cerebrospinal fluid motion in the cervical spine

**Introduction**: Many different 3D computational fluid dynamics (CFD) approaches have been utilized to simulate CSF dynamics in the spinal subarachnoid space (SSS) but little has been done to validate how well CFD reproduces the *in vivo* CSF dynamics. At present, time-resolved three directional velocity encoded phase-contrast MRI (4D PC MRI) can be regarded as the method that offers the best and most comprehensive insight into *in vivo* CSF dynamics. For that reason, it is likely the most suitable measurement method for comparison to CFD models. The aim of the present study was to carefully compare the CSF flow field in the cervical spine, measured by a) 4D PC MRI flow imaging and b) simulated by subject specific CFD, under a variety of CSF flow conditions (age and pathology). We hypothesized that important differences would be present between the CFD simulations and the 4D PC MRI measurements due to the presence of small anatomical structures within the CSF flow field and tissue motion.

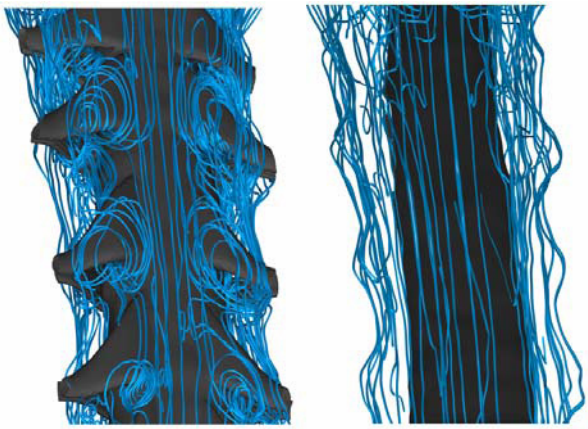



**Fig. 1 Streamline plots for a subject specific CFD simulation of CSF movement in the upper cervical spine including spinal cord nerve roots and denticulate ligaments (a) and without nerve roots and denticulate ligaments (b). Black structure is the spinal cord tissue. Dura is not pictured, but would be at the edges of where the streamlines are present in the pictures.**

**Methods:** We obtained 4D PC MRI in three healthy volunteers and four Chiari Malformation (CM) patients and compared the 4D PC MRI measurements to subject-specific CFD simulations conducted under two conditions 1) neglecting spinal cord nerve roots and denticulate ligaments and 2) including idealized spinal cord nerve roots and denticulate ligaments. The 4D PC MRI and CFD results were compared at nine axial planes along the cervical SSS in terms of a) peak CSF velocities in both cranial and caudal directions and b) visual interpretation of thru-plane velocity profiles.

**Results:** Our results support that i) fine anatomical structures had a great impact on CSF dynamics in terms of velocity profile, peak velocities and pressure drop and ii) marked differences in CSF dynamics were present between the 4D MRI measurements and CFD simulations. The 4D PC MRI peak CSF velocities were consistently greater than CFD both with and without the nerve roots and denticulate ligaments included. The differences in peak velocities were more pronounced in CM patients than in healthy subjects. In the upper cervical SSS of CM patients, the 4D PC MRI quantified stronger fluid jets than CFD. Visual interpretation of the 4D PC MRI thru-plane velocity profiles showed greater pulsatile movement of CSF in the anterior SSS in comparison to the posterior and reduction in local CSF velocities near nerve roots. Without spinal cord nerve roots and denticulate ligaments, the CFD velocity profiles were relatively uniform around the spinal cord for all subjects; with nerve roots and ligaments, velocity profiles were not uniform.

**Conclusion:** This study represents the first comparison of 4D PC MRI measurements to CFD of CSF flow in the cervical SSS. The results highlight the utility of 4D PC MRI for evaluation of complex CSF dynamics and the need for improvement of CFD methodology. Future studies are needed to investigate whether integration of fine anatomical structures and/or gross motion of the brain and spinal cord into the CFD model will lead to a better agreement between the 4D MRI and CFD results.

## Biography

Bryn Martin is the Director of the Conquer Chiari Research Center at the University of Akron. He completed his post-doctoral studies at the Swiss Federal Institute of Technology in Lausanne, Switzerland (2009-12) and Ph.D. at the University of Chicago (2008). His research interests are in CSF dynamics and pathophysiology of craniospinal disorders, medical instrumentation and cardiovascular biomechanics.

# Dr. Mark Quigley

## CSF Flow in Normal Adult and Pediatric Subjects: CSF Flow Abnormalities as a Diagnostic in Chiari I Patients

CSF velocity/flow at or near the plane of the foramen magnum exhibits pronounced variations in both space and time in both normal subjects and symptomatic Chiari I and Chiari Zero patients. Abnormalities in CSF velocities or flow obtained via PC-MR have been found to be extremely robust and reliable diagnostics, thereby making it possible to differentiate between persons with Chiari malformations whose symptoms are not related to their malformation, and genuine Chiari patients [1-4].

Objective recognition of flow abnormalities is best achieved using color scaled surface plots in which the z-axis represents the local CSF velocity. Chiari diagnosis based upon 2D gray-scale images of CSF velocity has been found to result poor specificity [5]. This is unquestionably a result of the long-known insensitivity of the eye to gray-scaled quantitative information, rather than an indication of shortcomings in CSF flow abnormalities as a diagnostic. The need for the proper visualization of quantitative data is crucial for the analysis of CSF velocity/flow data.

Significant qualitative differences in pediatric and adult CSF flow are seen both normal subjects and symptomatic patients. In normal subject, over about the age of 14 elevated CSF velocities (~20-30 mm/sec) are seen in two anterior regions off the paramedial line. These 'nodes' occupy 15% of the cross sectional area of the subarachnoid space, but carry 50-60% of CSF caudad flow. In symptomatic adults the nodal velocities are greatly elevated (50-80 mm/sec), thus forming "jets". In patients with more severe symptoms (~50%) bi-directional flow is seen, i.e., simultaneous movement of CSF in both the cephalad and caudad directions. Such bi-directional flow accounts for up to 25% of the total volume of CSF flow.

However, in normal pediatric subjects the nodes are replaced by a broad anterior band of elevated velocities. Symptomatic Chiari malformations are characterized by extremely elevated jet velocities, up to 200 mm/sec. Bi-directional flow is rather uncommon, and is seen only in children with very severe symptomatology. In addition, peak CSF velocities in children are somewhat higher that those seen in adults, falling rapidly to adult levels by the age of 20.

As a result, patient age is an important consideration in diagnosis. This is even more important in making a judgment on whether further surgical intervention will be effective, based on the extent to which CSF flow has returned to normal following surgery.

## Biography

Mark Quigley has a Ph.D. in Physics and worked in Chiari diagnosis research at the University of Wisconsin-Madison. He currently works in plasma physics research at the Naval Research Laboratory in Washington, DC.

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CONQUER CHIARI®

RESEARCH CENTER

Conquer Chiari is proud to announce the establishment of the world's first research laboratory dedicated solely to advancing the medical and scientific understanding of Chiari malformation in order to improve the experiences and outcomes of patients. Located at the University of Akron the CCRC will be a state of the art facility, staffed with distinguished researchers, working diligently to:

- Apply the latest engineering techniques and analyses to improve diagnoses and treatment options
- Leverage the Conquer Chiari Patient Registry to study the epidemiology and natural history of Chiari
- Foster collaborations with leading clinicians and scientists to advance the Conquer Chiari Research Agenda
- Act as a focal point for the Chiari research community and attract more researchers to the study of Chiari

Dr. Bryn Martin has been appointed the Director of the CCRC and has begun work on several initial projects:

- **Tonsil motion tool:** Pulsatile motion of the cerebellar tonsils has been thought to be elevated in Chiari I (CMI) patients. The aim of this study is to 1) noninvasively quantify the difference between tonsillar motion (TM) in symptomatic CMI patients and age/gender matched healthy controls and 2) further quantify differences in TM pre and post decompression surgery. TM will be assessed by development of a novel tool that utilizes motion sensitive 3D MRI morphology scans. We hypothesize that TM will be greater in Chiari patients than healthy controls and that TM will be reduced post successful decompression surgery. If successful, the TM tool will have potential to help assess CMI disease states and surgical success.
- **Nerve damage tool:** The extent and time course of nerve damage in Chiari I malformation (CMI) and syringomyelia (SM) is difficult to assess. The aim of this study is to 1) develop a nerve damage (ND) tool based on noninvasive MRI diffusion tensor imaging (DTI) and magnetization transfer (MT) and 2) demonstrate the ND tool on SM and CMI patients with clinical symptoms versus age/gender matched healthy controls. We hypothesize that ND will be detectable in patients versus healthy controls due to alterations in the spinal cord properties such as fraction of anisotropy in diffusion. If successful, the ND tool will have potential to help assess SM and CMI disease states and surgical success.
- **HydroSpine:** A number of engineering groups have simulated CSF hydrodynamics in the spine under varying levels of complexity. However, none of these simulations have been validated. The aim of this study is to develop a hydrodynamics simulation of the spine (HydroSpine) that includes enough anatomical detail to accurately simulate the spinal hydrodynamics and validate this tool on a subject specific basis with in vivo MRI measurements. We will then use HydroSpine as a platform to assess the impact of anatomical structures such as presence of Chiari malformation, denticulate ligaments, spinal cord nerve roots and arachnoid trabeculae on CSF hydrodynamics. This tool will help to reveal important information about the hydrodynamic environment of the spine that could identify new treatment possibilities. HydroSpine also has potential to help design intrathecal catheters and/or spinal shunts.
- **Molecular Processes Associated with Syringomyelia:** Currently, the cellular/molecular initiation and progression of syringomyelia are not entirely understood. This study will utilize an animal model of posttraumatic syringomyelia as a beginning investigation toward understanding the associated effectors and pathways to lay the groundwork for future treatment strategies. The work will be directed by Dr. Nic Leipzig, who has previously developed potential approaches to deliver biomaterials, proteins and cells for treatment of syringomyelia. The hypothesis is that syringomyelia will result in significant upregulation of inflammation and astrocytic associated genes, with a secondary goal to uncover new pathways related to hypoxia and mechanotransduction. A published experimental rat syringomyelia model with μCT will be used to study the progression of the syrinx over 6 weeks. At the final time point, global gene expression analysis (via transcriptome sequencing (RNA-seq)) and histology will be performed and compared to control animals. For the first time, these results will provide a quantitative picture of all transcriptional changes that occur following syringomyelia, providing invaluable data for researchers and clinicians.

The Conquer Chiari Research Center welcomes both collaborations and visiting researchers and scholars.

To learn more about working with the CCRC, contact Dr. Martin at director@chiari-research.org.

Column of Hope

Chiari & Syringomyelia Research Foundation

What is Column of Hope?

Established in 2004, Chiari & Syringomyelia Research Foundation, DBA Column of Hope (COH), is a Buffalo, NY, all volunteer, 501(c)(3) organization. With its small, focused budget, it has made tremendous progress toward finding the causes of two debilitating neurological disorders, Chiari malformation (CM) and syringomyelia(SM).

COH partners with the "best and brightest" individuals from its own medical, scientific and business networks to find and assist high quality CM/SM researchers around the globe. COH has relatively low overhead, allowing it to dedicate 100% of the net proceeds from its annual Gala to its research efforts. COH funded research has produced eight articles published in highly regarded peer reviewed journals, including a cover article of the Journal of Neurosurgery. More exciting studies are scheduled to be published in the upcoming few months. COH's model for delivering successful research is simple:

- COH finds high quality researchers, wherever they are in the world.
- COH works collaboratively with these researchers, using the translational research skills of its volunteer team, led by the well known stroke neurosurgeon and inventor, Lee R. Guterman, PhD, MD.
- COH supports its research by finding top quality partners to assist its researchers in eliminating bottlenecks.
- Most importantly, COH has tremendous supporters, who provide the funds and encouragement needed to continue to deliver ground breaking research.

For more information, go to www.columnofhope.org or email mark_kane@columnofhope.org.

# Notes