COOPERATIVE STUDIES ON BRAIN INJURY DEPOLARISATION

16th ANNUAL MEETING, COSBID 2014

October 23rd- 24th

MASSACHUSETTS GENERAL HOSPITAL
185 CAMBRIDGE ST
BOSTON, MA • 02114

Introduction

Welcome to the Cooperative Studies on Brain Injury Depolarization (COSBID) 16th Annual Meeting, Boston. COSBID is an international cooperation of clinical and basic science neurology researchers working in various participating centers across Europe and North America.

The goal of COSBID is to study mechanisms of secondary brain injury, most notably the significance of repeated depolarizations in the acutely injured brain for local tissue damage and the long-term outcome of patients.

The overarching purpose of our work is to investigate whether treatment of brain injury depolarizations may represent a potential target for neuroprotection.

Ongoing clinical studies led by our collaborators address conditions including:

1. Traumatic brain injury (TBI);
2. Aneurysmal subarachnoid hemorrhage (SAH);
3. Malignant hemispheric stroke (MHS);
4. Intracerebral hemorrhage (ICH);

At this year's meeting, we will hear updates from ongoing and recently concluded clinical studies, and review the latest data on cortical depolarizations and multimodal neuromonitoring in clinical and experimental models of acute brain injuries.

Program Committee

Cenk Ayata, MD
Jed Hartings, PhD
Eric S. Rosenthal, MD
M. Brandon Westover, MD, PhD

Steering Committee

Jens Dreier, MD, PhD
Martin E. Fabricius, MD, DMSc
Rudolf Graf, MD, PhD
Jed Hartings, PhD
Bill Shuttleworth, PhD
Oliver Sakowitz, DM
Anthony Strong, DM

Program Coordinator

Emily Boyle
55 Fruit Street, Boston MA 02114
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Meeting Location

Massachusetts General Hospital
Simches 3rd Floor Auditorium - Room 3110
185 Cambridge Street, Boston MA 02114
(See enclosed map on Page 14)

If walking from the main hospital building, exit from the Wang Lobby, turn left on Parkman Street and enter through the door straight ahead after crossing Blossom Street (see image below). Walk up the stairs to Blossom Street Lobby, exit straight ahead and turn left. The Simches building will be on your left.

or

Enter through Charles River Plaza from Cambridge Street, next to Whole Foods Supermarket.

Registration

- Early registration (before October 1st): $50
- Regular Registration (after October 1st): $75
- Junior Researcher/Trainee Registration: Free

On-site Registration/Check-in

Lunder Building 6th Floor Atrium (See enclosed map on page 14)
Thursday, October 23rd
8:00am-9:15am

All attendees **must** check-in on Thursday morning to collect name badges and programs, and pay registration fees (if not already received) by check or cash. Attendees may not be able to gain access to the Simches Building without proper identification. If you are unable to attend registration on Thursday morning, **please contact Emily Boyle (ejboyle@partners.org) to obtain your badge.**

COSBID Dinner

Mamma Maria Restaurant (See enclosed map on Page 15)
3 North Square, Boston, MA 02113
Thursday, October 23rd
6:30-10:00pm

Please note that due to strictly enforced capacity limits at Mamma Maria, we have asked that attendees RSVP in advance (via the online registration form) if planning to attend the group dinner on Thursday evening. We regret that we will not be able to accommodate any 'day-of' additions to the guest list, as our expected party has already reached the maximum size that the restaurant can allow.

WiFi

Network: phspiaguest
Select network and then load webpage to accept terms.

Thursday, October 23rd

8:00-9:15 Registration and Breakfast (Lunder 6 Atrium)

9:30-9:45 Welcome and Introductions (Simches 3 Auditorium)

Cenk Ayata, Eric Rosenthal, Brandon Westover

9:45-11:25 Session I (Simches 3 Auditorium)

Moderator: Cenk Ayata

9:45-10:10 **Neuronal and Astroglial Structural Integrity During Cortical Spreading Depolarization**
Sergei Kirov

10:10-10:35 **Suppression of spreading depolarization and stabilization of dendritic spine morphology by GLYX-13, a NMDA receptor glycine-site functional partial agonist**
Patric Stanton

10:35-11:00 **Blood-Brain Barrier Pathology and Changes in Network Excitability: The Chicken and Egg Dilemma**
Alon Friedman

11:00-11:25 **Neurovascular coupling in the injured brain: Does blood-brain barrier breakdown play a role in disturbed neurovascular coupling and associated damage**
Jens Dreier

11:30-1:30 Lunch (See Enclosed Suggestions)

1:30-3:35 Session II (Simches 3 Auditorium)

Moderator: Jed Hartings

1:30-1:55 **Cross Talk Between Cells of the Neurovascular Unit**
Eng Lo

1:55-2:20 **Venous K+ clearance during spreading depolarizations**
Jessica Seidel

2:20-2:45 **Inverse Neurovascular Coupling to Cortical Spreading Depolarizations in Severe Brain Trauma**
Jason Hinzman

2:45-3:10 **The Effect of Ketamine on Vascular Reactivity during Spreading Depolarization in Gyrencephalic Swine Cortex**
Renan Sanchez-Porras

3:10-3:35 **Local blood supply modulates CBF response to CSD**
Heiko Backes

3:35-4:05 Break

Thursday, October 23rd

4:05-5:20 Session III (Simches 3 Auditorium)

Moderator: Eric Rosenthal

4:05-4:30 **CSD Autodetection**
Andrew Carlson

4:30-4:55 **Proposal for non-invasive detection of cortical spreading depression**
Steve Jones

4:55-5:20 **CSD detection with depth electrodes**
Anthony Strong

Friday, October 24th

8:15-9:30 Session IV (Simches 3 Auditorium)

Moderator: Jens Dreier

8:15-8:40 **2P pO2 Microscopy**
Sava Sakadzic

8:40-9:05 **Spreading depolarization in experimental cerebral ischemia: what can we learn by in vivo multimodal imaging?**
Eszter Farkas

9:05-9:30 **NIRS**
Juliette Selb

9:30-10:00 Break

10:00-11:15 Session V (Simches 3 Auditorium)

Moderator: Tony Strong

10:00-10:25 **Supply-demand mismatch transients trigger injury depolarizations**
Cenk Ayata

10:25-10:50 **Spreading Depolarizations in Patients with Intracerebral Hematoma**
Raimund Helbok

10:50-11:15 **Irregular movement patterns of spreading depolarization occur in the gyrencephalic brain**
Edgar Santos-Marcial

11:15-1:15 Lunch (Catered in Yawkey 4-820, See Map on Page 14)

11:45-12:45 **Oral Abstract Presentations (see listing on page 7 for details)**

Friday, October 24th

1:30-2:45 Session VI (Simches 3 Auditorium)

Moderator: Brandon Westover

1:30-1:55 **CSD in Surface EEG of Acutely Brain Injured Patients**
Jan Claassen

1:55-2:20 **Leão's spreading depression in continuous electroencephalography of brain trauma**
Jed Hartings

2:20-2:45 **Update on nonconvulsive seizures in the critically ill: prevalence, consequences, and relation to CSD**
Lawrence Hirsch

2:45-3:00 Break

3:00-4:30 Investigator Satellite Session: Simches 3 Conference Room

Technologies and Methods in Research

Moderator: Eric Rosenthal

Technology Presentations (10 min each, including Q&A)	**3:00-3:10**	*Moberg, Inc.*
	3:10-3:20	*Natus Medical, Inc.*
	3:20-3:30	*Hemedex, Inc.*
	3:30-3:40	*PMT, Corp.*
	3:40-3:50	*Ad-Tech Medical Intrument,Corp.*
	3:50-4:00	*Raumedic*
Panel discussion	**4:00-4:30**	***Moderated group discussion among investigators and manufacturers***

4:30-4:45 Break

4:45-5:15 Session VII (Simches 3 Auditorium)

Moderator: Martin Fabricius

5:00-5:15 **Future Initiatives: Center TBI Update**
Oliver Sakowitz and Martin Fabricius

5:15-6:00 Forum: How should a clinical trial targeting Injury Depolarization Be Designed? (Simches 3 Auditorium)

Forum Moderator: Cenk Ayata

1. Is monitoring and confirmation of injury depolarizations required?
2. Best pharmacological or physiological candidate interventions?
3. Multicenter/Multinational structure?
4. Funding?

11:45-12:45 Abstract Presentations (Yawkey 4-820, See Enclosed Map)

Moderator: Jessica Seidel

11:45-11:55 **Does ischemia induce spreading depolarization by converting the Na^+/K^+ pump into a channel?** (Page 8)

David Andrew (Queens University)

11:55-12:05 **Adenosine contributes to coupling of metabolism with depression of activity following SD** (Page 9)

Britta E. Lindquist (University of New Mexico)

12:05-12:15 **Consequences of cortical spreading depolarizations on cerebral blood flow and metabolism: comparison of healthy and traumatized cortex** (Page 10)

Baptiste Balanca (Lyon Neuroscience Research Center)

12:15-12:25 **Dose dependent suppression of cortical spreading depolarizations by S-ketamine in a patient with hypertensive intracerebral hemorrhage** (Page 11)

Alois Schiefecker (Innsbruck Medical University)

12:25-12:35 **Prediction of infarcted tissue by intraoperative laser speckle imaging in patients undergoing decompressive craniectomy after malignant hemispheric stroke** (Page 12)

Nils Hecht (Charité University Medicine Berlin)

12:35-12:45 **Spreading depolarizations are associated with decreased oxygen availability in human malignant hemispheric stroke** (Page 13)

Nora Sandow (Charité University Medicine Berlin)

Does ischemia induce spreading depolarization by converting the Na^+/K^+ pump into a channel?

R. David Andrew and Danielle Kim, Centre for Neuroscience Studies, Queen`s University, Kingston, Canada.

The gray matter of the higher brain undergoes spreading depolarization in response to ischemia, which increases metabolic demand and thereby promotes acute neuronal injury. The molecular mechanism linking neuronal failure of the Na^+/K^+ pump to the near-immediate onset of a massive and propagating inward current driving spreading depolarization has remained a mystery. Blockade of any conventional voltage- or ligand- gated channel does not prevent this ischemic or "anoxic" depolarization (AD) which propagates across gray matter. Recently our laboratory became aware of a marine poison whose molecular action is well characterized but whose effects on brain tissue have escaped scrutiny by neuroscientists. This toxin could provide insight as to how ischemia acutely damages neurons at the molecular level.

Palytoxin (PTX) specifically binds the Na^+/K^+ ATPase molecule at incredibly low concentrations, converting it from an ATP-requiring transporter to an open cationic channel. The result is sudden neuronal Na^+ influx and K^+ efflux. The double jeopardy of pump failure with the induction of a strong inward current should induce dramatic AD-like activity at very low concentrations. And indeed we show that bath application of 1 to 100 nM PTX to live coronal brain slices induces a propagating depolarization remarkably similar to the AD induced by oxygen/glucose deprivation (OGD), as shown by light transmittance (LT) imaging. We tested if 10 nM PTX mimicked other effects of OGD. In neocortex, as the elevated LT front passed by an extracellular recording pipette a distinct negative DC shift was recorded, indicating strong depolarization of cells at the electrode, whether induced by OGD or PTX. Both treatments induced strong spreading depolarization in the same higher brain regions and weaker events in lower brain gray matter. We also tested two drugs (dibucaine and carbetapentane) that delay AD onset induced by OGD. At similar concentrations the spreading depolarization induced by PTX was likewise delayed. All of the above findings support our proposal that, like most biological poisons, palytoxin mimics (and takes advantage of) a natural process. In this case the process could be ischemia, where low ATP conditions might open the Na^+/K^+ pump to evoke spreading depolarization.

Supported by the Heart and Stroke Foundation of Canada.

Title: Adenosine contributes to coupling of metabolism with depression of activity following SD

Authors: Britta E. Lindquist and C. William Shuttleworth

Affiliation: University of New Mexico School of Medicine, Department of Neurosciences, Albuquerque, NM, USA

Abstract: The duration of electrocorticographic (ECoG) depression is a prognostic indicator of vulnerable tissue undergoing spreading depolarization (SD). The mechanisms linking SD to different phases of ECoG depression are incompletely understood. We have previously demonstrated in hippocampal brain slices that there are two distinct mechanisms of depression resulting from SD: a short-lasting axonal depolarization block, and a longer-lasting synaptic depression mediated by adenosine A1 receptor activation (*Neuroscience* (2012) PMID 22864185). Here, we tested the roles of depolarization block and adenosine A1R activation *in vivo*, during cortical spreading depressions elicited in anesthetized C57Bl/6 mice. Consistent with our prior results, we found that depolarization block (measured in efferent transcallosal projections) was short (55.9±6.2 s) and approximately matched the DC shift duration, whereas depression of spontaneous electrocorticographic (ECoG) activity was longer lasting (393.8±38.9 s, $p<0.0001$ ANOVA). We examined adenosine-dependent depression by focally applying A1R-targeting drugs and evaluating their effects on spontaneous and evoked electrocortical activity. A1R antagonist DPCPX (30 μM) shortened ECoG depressions by 16±5% ($p<0.01$, n=7 animals), whereas the adenosine deaminase (ADA) inhibitor deoxycoformycin (100 μM) increased ECoG depressions by 48±33% ($p=0.01$, n=5 animals). Together, these results are consistent with a role for adenosine A1Rs in the depression of ECoG, and suggest that deamination may be one adenosine clearance mechanism regulating the duration of depression. Adenosine is well positioned to link the metabolic burden of SD to synaptic depression in vulnerable tissue, and indeed adenosine accumulation correlates with the duration of ECoG depression in injury models (*JCBFM* (2014) PMID 25160669). These findings have potential applications for the development of biomarkers indicating SD frequency or severity, in patients without craniotomy. We will also discuss other possible consequences of adenosine accumulation such as effects on immune or vascular targets.

Consequences of cortical spreading depolarizations on cerebral blood flow and metabolism: comparison of healthy and traumatized cortex.

Baptiste BALANCA*, Thomas LIEUTAUD¥, Anne MEILLER†, Stéphane MARINESCO*¥†.

*CRNL Team Waking, ¥CRNL Team Tiger, †CRNL Neurochem platform. UCBL, Lyon1. Université de Lyon, France

Introduction: Human studies recording cortical spreading depolarizations (CSDs) reported heterogeneous results regarding cerebral blood flow (CBF) and metabolism. This could be related to different basal conditions of the cortex onto which CSDs spread. In our study, we intend to compare the microvascular and metabolic consequences of CSDs, when triggered by KCl administration onto an unharmed cortex or occurring after severe traumatic brain injury (TBI).

Methods: Wistar rats were anesthetized with isoflurane in a mixed air with oxygen (30%). CSD were either triggered by cortical KCl apposition (KCl group; n=6 in for each probe) or occurred spontaneously during the 5 h recording following a severe (3.8 ATA) lateral fluid percussion brain injury (LFPI group, n=5 for each probe). Animals were intubated prior and artificially ventilated after LFPI until they recovered spontaneous breathing. Animals were equipped with a 1 mm laser Doppler flowmeter (LDF) probe on the cortex for cerebral blood flow measurements. Electrocorticogram was recorded using a silver chloride wire within a glass micropipette (3-5 µm tip); brain oxygen concentration (tPO2) using a Clark type electrode (10 µm tip); and brain glucose and lactate concentrations using microelectrode biosensors (40 µm tip) consisting in a platinum wire inserted in a glass micropipette and covered with a specific oxidase.

Results: During the 5 hours recording following severe LFPI 72.6% of rats displayed CSDs (2.5 ± 1.7 per 5h post TBI). CSDs induced an increase in LDF in both groups (KCl +139% ± 98 *vs* LFPI +95% ±82, p=0.25), followed by a sustained decrease after LFPI (KCl +4%± 13 vs LFPI -15% ± 8, p=0.004). CSDs also had dramatically different effects on brain tissue oxygenation: tPO_2 displayed a 7.1 ± 4.5 mmHg increase following KCl, whereas it decreased by -22.6 ± 19.6 mmHg (p=0.001) after LFPI. Moreover tPO2 remained significantly decreased after LFPI but not after KCl apposition (LFPI -10.8 ± 7.8 mmHg vs KCl +1.45 ± 2.7 mmHg, p=0.016). Brain energy metabolism evidenced by glucose and lactate extracellular concentrations was also differently impacted by CSDs. Brain glucose displayed a larger decrease after LFPI (-1.45 ± 0.87 mM *vs* KCl -0.7 ± 0.45mM, p=0.068). In addition, whereas lactate increased in the KCL group, it decreased significantly after LFPI (KCl +0.52 ± 0.58mM vs LFPI -0.39 ± 0.55mM; p=0.004).

Conclusion: CSDs induced by KCl on a healthy cortex produced a hyper-metabolism with a hyperemia that was consistent with other studies. The specific pattern observed after LFPI, characterized by a drop in tPO2, brain glucose and lactate associated with progressive decrease in LDF suggested that CSDs tended to induce a metabolic crisis that could favor further brain injury during the hours or days following TBI. Overall, our data confirm the view that CSDs can induce dramatically different effects depending on whether they spread on a healthy or injured tissue.

Dose dependent suppression of cortical spreading depolarizations by S-ketamine in a patient with hypertensive intracerebral hemorrhage

AJ. Schiefecker[1], M. Kofler[1], R. Beer[1], B. Pfausler[1], P. Lackner[1], G. Broessner[1], F. Sohm[2], M. Mulino[2], C. Thome[2], P. Rhomberg[3], E. Schmutzhard[1], R. Helbok[1]

[1]Department of Neurology, Division of Neurocritical Care, Innsbruck Medical University, Austria
[2]Department of Neurosurgery, Innsbruck Medical University, Austria
[3]Department of Neuroradiology, Innsbruck Medical University, Austria

Background: Cortical spreading depolarizations (CSDs) are characterized by a propagating loss of neuronal ion homeostasis and are believed to contribute to secondary brain injury. Recent data suggest that CSDs can be modulated by sedatives and may be suppressed by ketamine in humans. Here we report a patient with hypertensive intracerebral hemorrhage (ICH) developing clusters of CSDs.

Case: A 59 year-old man with a medical history of hypertension and atrial fibrillation was admitted to our neurological intensive care unit. He presented with left-sided hemiplegia and an initial Glasgow Coma Scale (GCS) of 10. Cerebral computed tomography revealed an intracerebral hematoma (ICH; 31 ml) with perifocal edema (23 ml). The same day the patient worsened secondary to rebleeding and perifocal edema growth and required mechanical ventilation. Hematoma evacuation and insertion of multimodal neuromonitoring devices, including subdural strip electrodes for electrocorticography (ECoG), was performed. 45 CSDs occurred during 154 hours with EcoG monitoring. Clusters of CSDs with progressive reduction of cortical activity were observed while the patient was on 0.28 mg/kg/h midazolam and 3 µg/kg/h sufentanil. A bolus of S-ketamine (50 mg) followed by continuous infusion of 0.7 mg/kg/h led to recovery of cortical activity without further occurrence of CSDs. When ketamine infusion was stopped, clusters of CSDs (1 per hour) reappeared. A dose dependent effect of S-ketamine was observed as a continuous infusion of 0.2 mg/kg/h ketamine partially (frequency 0.5 per hour) and a dose of 0.4-0.7 mg/kg/h S-ketamine completely suppressed the occurrence of CSDs. Sequential magnetic resonance imaging scans were performed at 5, 12 and 16 days after ICH, respectively, revealing progressing subcortical and cortical T2-hyperintensities adjacent to the subdural strip between day 12 and day 16. The patient had a favorable clinical course with a modified Rankin Scale of 4 at 3 months.

Conclusion: Our observation suggests a dose dependent effect of S-ketamine on the occurrence of CSDs. The progression of the cortical/subcortical lesion may be associated with clusters of CSDs. The impact of ketamine as potential treatment for CSDs and the clinical significance of CSDs occurring as clusters after ICH require further studies.

Character count: 2267

Prediction of infarcted tissue by intraoperative Laser Speckle Imaging in patients undergoing decompressive craniectomy after malignant hemispheric stroke

Nils Hecht, Marc-Michael Müller, Nora Sandow, Alexandra Pinczolits,
Peter Vajkoczy, Johannes Woitzik
Department of Neurosurgery and Center for Stroke research Berlin (CSB),
Charité – Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin

Objective
Laser Speckle Imaging (LSI) can be used for non-invasive and direct assessment of cortical perfusion. The purpose of this study was to establish positive and negative predictive values for LSI-specific perfusion thresholds of infarcted and non-infarcted tissue in the human brain.
Methods
Intraoperative LSI was performed in 22 patients undergoing decompressive craniectomy (DC) for treatment of malignant hemispheric stroke (MHS). Infarct size and configuration was assessed by magnetic resonance imaging (MRI) and a 3-dimensional model reconstruction of the cortical surface (defined by MPRAGE) including the infracted cortical tissue (defined by DWI/ADC) was performed. Next, a color-coded laser speckle blood flow image was superimposed onto the MRI reconstruction and the infracted and non-infarcted areas were traced onto the laser speckle image. Regions of interest (ROIs) were positioned over the laser speckle image and LSI-specific relative cortical perfusion was calculated within the ROIs of the infarcted and non-infarcted area. LSI-specific perfusion values (CBF-Flux) were normalized to 100% and relative frequency distributions of the cortical perfusion within the infracted and non-infarcted area were calculated for each patient. Finally, cumulative probability curves were computed and positive (at least 95% chance of infarct) and negative (at least 95% chance of non-infarct) prediction limits for eventual infarction were determined.
Results
In all 22 patients, LSI permitted immediate real-time visualization and measurement of relative CBF in excellent image quality and high spatial-temporal resolution. Positive and negative prediction limits of infracted tissue were determined at 40% and 110% of baseline perfusion, respectively. Of the exposed cortical surface area, 61.7±24% was determined as infracted (below the 40% limit) compared to 11.2±9% as non-infarcted (above the 110% limit) and 27.2±16% as tissue with perfusion between 40% and 110%.
Conclusion
LSI appears to be a valuable tool to sensitively predict infarcted and non-infarcted tissue in excellent spatial resolution during neurosurgical procedures.

Spreading depolarizations are associated with decreased oxygen availability in human malignant hemispheric stroke.

Sandow N[1,2], Pinczolits A[1,2], Hecht N[1,2], Vajkoczy P[1,2], Major S[2,3], Winkler M[2,3], Dreier J[2,3], Woitzik J[1,2]

[1] Department of Neurosurgery, Charité Universitätsmedizin Berlin, Germany

[2] Center of Stroke Research (CSB), Charité Universitätsmedizin Berlin, Germany

[3] Departments of Neurology and Experimental Neurology, Charité Universitätsmedizin Berlin, Germany

Objective: Cortical spreading depolarizations (CSDs) influence cortical oxygen availability (O_2) by changes in local blood flow and augmented metabolism. Intraoperative laser speckle data of cortical cerebral blood flow in patients suffering from malignant hemispheric stroke (MHS) revealed that CSDs coincide with hyperemic flow responses in most cases. Data of O_2-availability during CSDs occurring in patients with MHS is still missing. We designed this study to evaluate the effect of CSDs on O_2-availability in patients with MHS during a 7 day monitoring period after ictus.

Methods: In 7 patients with MHS and clinical decision for hemicraniectomy a 6-contact platinum subdural ECoG recording strip (Ad-Tech Medical, Racine, WI, USA) was positioned over the ipsilateral frontal cortex and a Clark-type probe (Licox CC1-SB, IntegraNeuroscience, Andover, UK) was placed next to the ECoG-strip electrode in an oblique fashion to assess cortical tissue partial pressure of oxygen ($ptiO_2$). $P_{ti}O_2$ values were continuously recorded and analyzed. Inverse monophasic, monophasic increase, biphasic and inverse biphasic (initial decrease and secondary increase) $p_{ti}O_2$ changes were registered.

Results: We found a total of 219 CSDs in in 7 patients. In 89/219 CSDs (40.6%) $p_{ti}O_2$ changes occurred in spatial and temporal correlation to the CSD. 78 % of all O_2-responses correlated with a monophasic decrease, 21 % were associated with a biphasic change and only 1% was associated with a monophasic increase.

Summary and Conclusion: Clear spatial and temporal associations of $p_{ti}O_2$ responses with EcoG events were found in 40% of CSDs in 7 patients suffering MHS. Predominantly, inverse monophasic or inverse biphasic $p_{ti}O_2$ changes were detected, concluding that hyperemic changes in cerebral blood flow may not be sufficient to anticipate augmented metabolism during CSD in MHS leading to decreased oxygen availability.

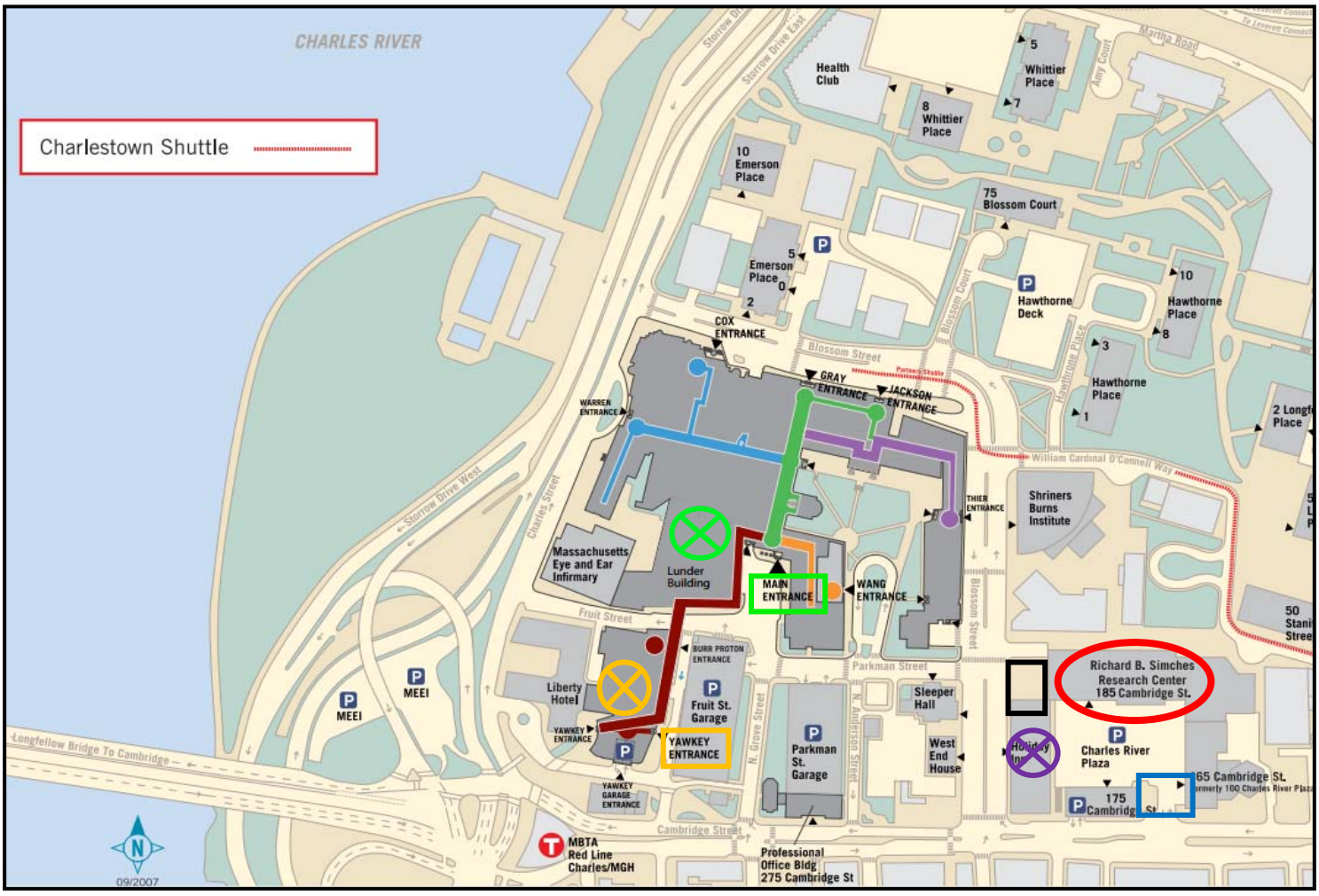
MGH Main Campus Map

= **Simches 3 Auditorium**
185 Cambridge Street, Boston 02114
Enter from Parkman St. or from Cambridge St.

= **Lunder 6 Atrium (Registration and Check-in)**
55 Fruit St, Boston 02114
Enter through Main Entrance

= **Yawkey 4-820 (Friday lunch and Abstract Presentations)**
Enter through Yawkey Entrance

= **Wyndham Boston Beacon Hill Hotel**



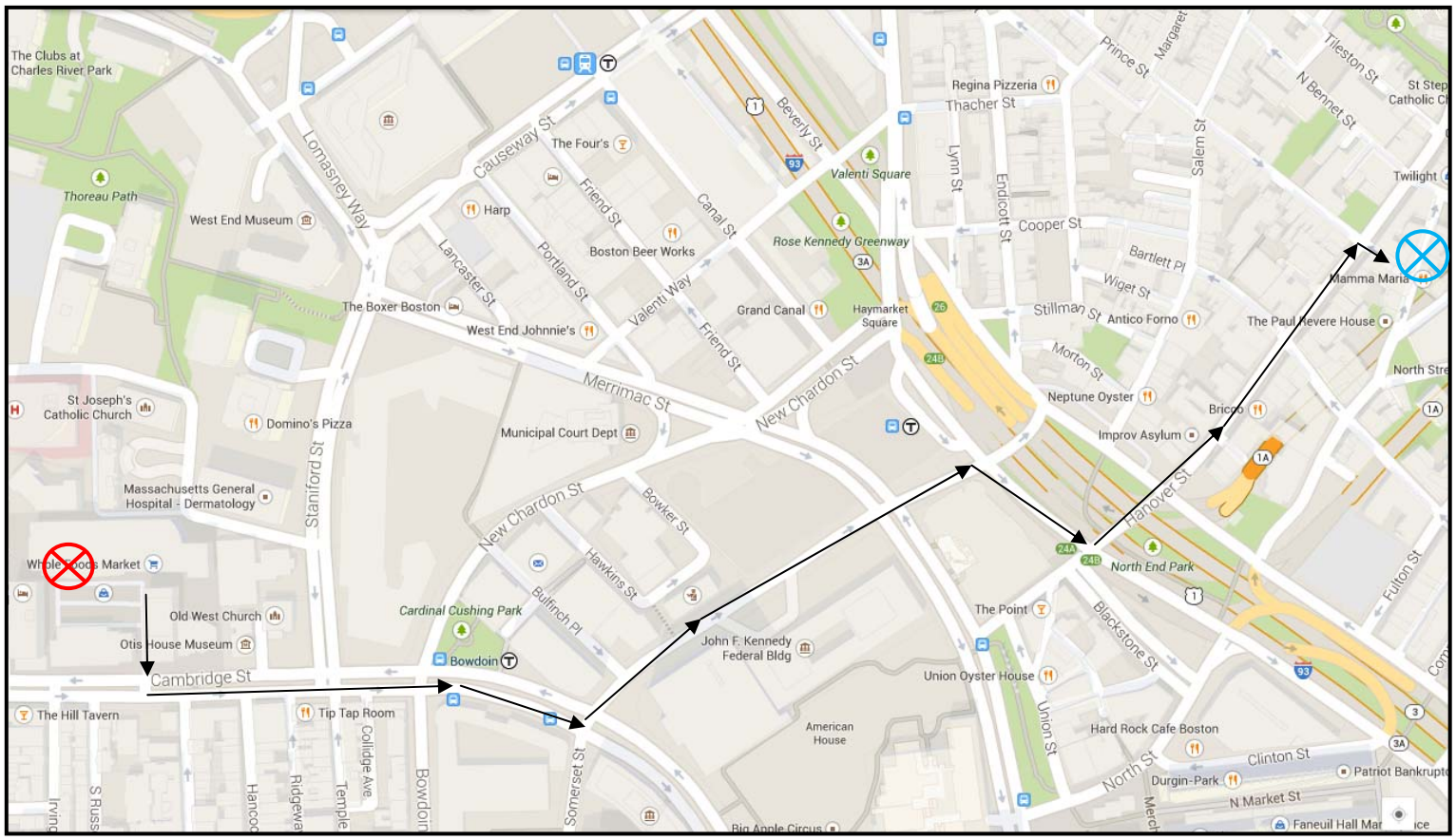
Directions to COSBID Dinner – Mamma Maria Restaurant

Thursday, October 23rd
6:30-10:00pm

= Mamma Maria Restaurant (approach from Hanover St.)
3 North Square, Boston MA 02113
(617) 523-0077

= Simches 3 Conference room
185 Cambridge St, Boston MA 02114

*Estimated walking time from MGH is 15 minutes



Local Restaurants

1. **Tip Tap Room**
   138 Cambridge St, 02114
2. **Seoul**
   156 Cambridge St, 02114
3. **The Hill Tavern**
   228 Cambridge St, 02114
4. **Fin's Suchi&Grill**
   240 Cambridge St, 02114
5. **Clink (Liberty Hotel)**
   215 Charles St, 02114
6. **King & I**
   145 Charles St, 02114
7. **Panificio Bistro & Bakery**
   144 Charles St, 02114
8. **Artu On Charles Street**
   89 Charles St, 02114
9. **Lala Rokh**
   97 Mt Vernon St, 02108
10. **Paramount Restaurant**
    44 Charles St, 02114
11. **75 Chestnut**
    75 Chestnut St, 02108
12. **Grotto**
    37 Bowdoin St, 02114
13. **21st Amendment**
    150 Bowdoin St, 02108
14. **Scollay Square**
    21 Beacon St #1, 02108