

# **From Research to Write-Up**

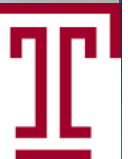
---

**Dianne Langford, PhD**

**Assistant Dean Research, LKSOM**

**[tdl@temple.edu](mailto:tdl@temple.edu)**

---





# Getting Started

---

**Identify a Research Question**

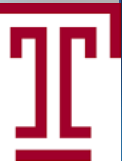
**Gap in Knowledge**

**Limitation in Patient Care**

**Diagnosis**

**Treatment**

**Prognosis**



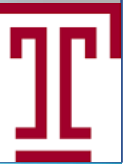
# What has been done already??

---

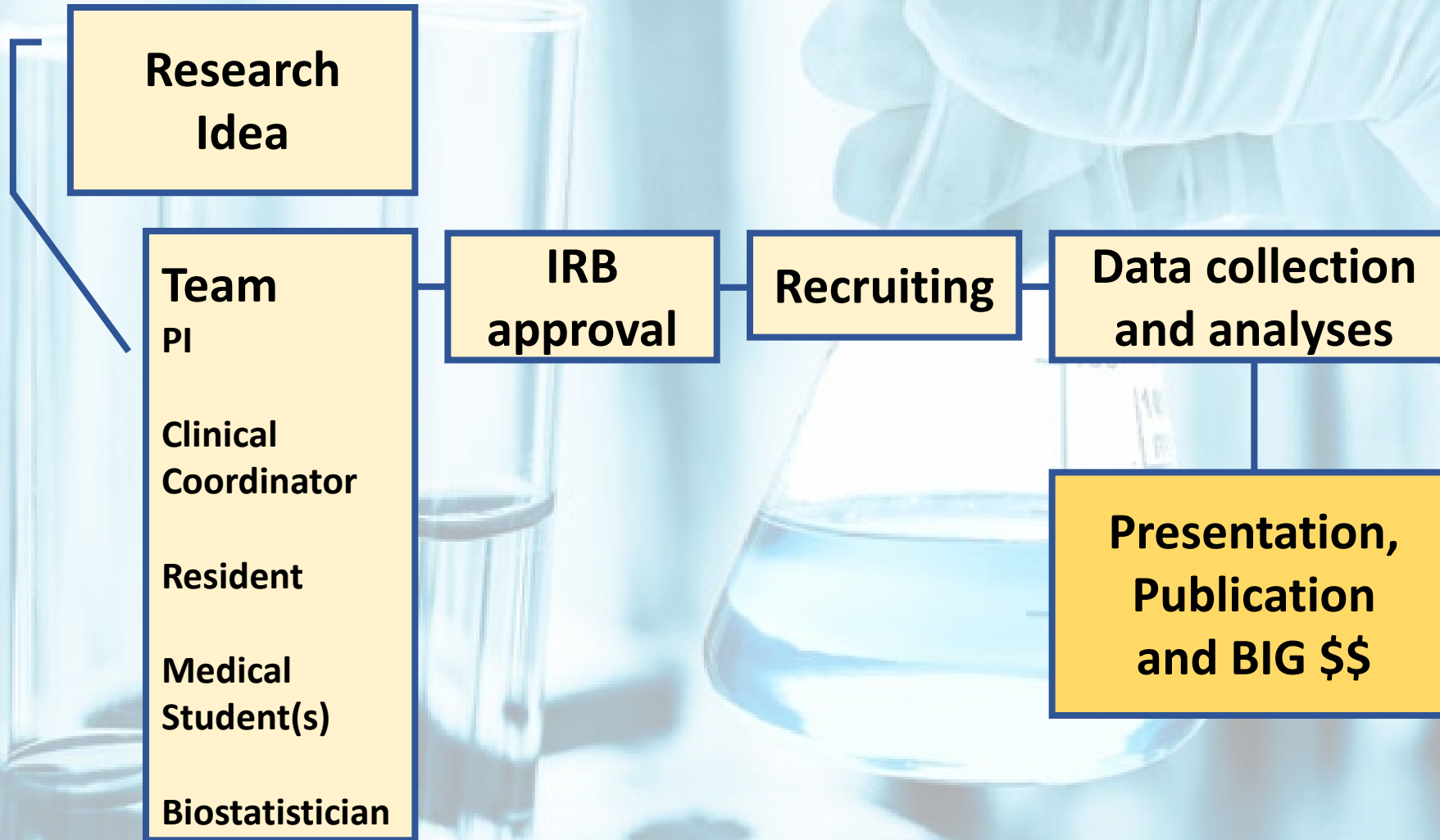
**To write the RATIONALE:**

**Review the Current SoC**

**Review the Literature**



# From Research to Write-Up



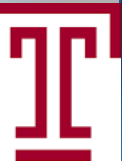
# IRB

---

**Start with a template/example of a successful protocol  
(Approved)**

**Difficult the first time navigating the online process**

**David Comalli, PhD**  
IRB Assistant Director  
Direct 215-707-7792  
Email [David.Comalli@temple.edu](mailto:David.Comalli@temple.edu)



# Summary/Abstract

---

## Identify the problem

Diagnosis  
Treatment  
Prognosis

## Rationale for Study

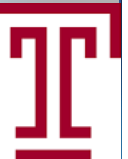
Previous research

## Study Objective

Brief Design  
Hypothesis

Clinical  
Significance

Build Research Team



# From Research to Write-Up

**Research  
Idea**

**Team  
PI**

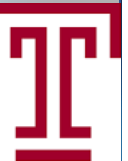
**Clinical  
Coordinator**

**Resident**

**Medical  
Student(s)**

**Biostatistician**

**TEAM &  
TIME!!!**



# From Research to Write-Up





**Study Objective**  
**Brief Design**  
**Hypothesis**



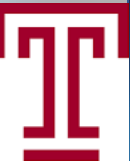
**Build Research Team**



**Biostats**

**Assays**  
**Measures**

**Funding**  
**Source**





## Statistical analysis

### **Susan G. Fisher, PhD, MS**

Chair, Department of Clinical Sciences

Professor, Clinical Sciences

Associate Cancer Center Director for Community Outreach and Health

Disparities, Fox Chase Cancer Center

[susan.fisher@temple.edu](mailto:susan.fisher@temple.edu)

### **Huaqing Zhao, PhD, MS**

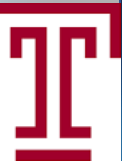
Associate Professor, Clinical Sciences

[zhao@temple.edu](mailto:zhao@temple.edu)

### **Daohai Yu, PhD, MS**

Professor (Teaching/Instructional), Clinical Sciences

[dYu@temple.edu](mailto:dYu@temple.edu)



**Study Objective**  
**Brief Design**  
**Hypothesis**



**Build Research Team**



**Biostats**



**Assays**  
**Measures**

**Funding**  
**Source**





**Assays  
Measures**



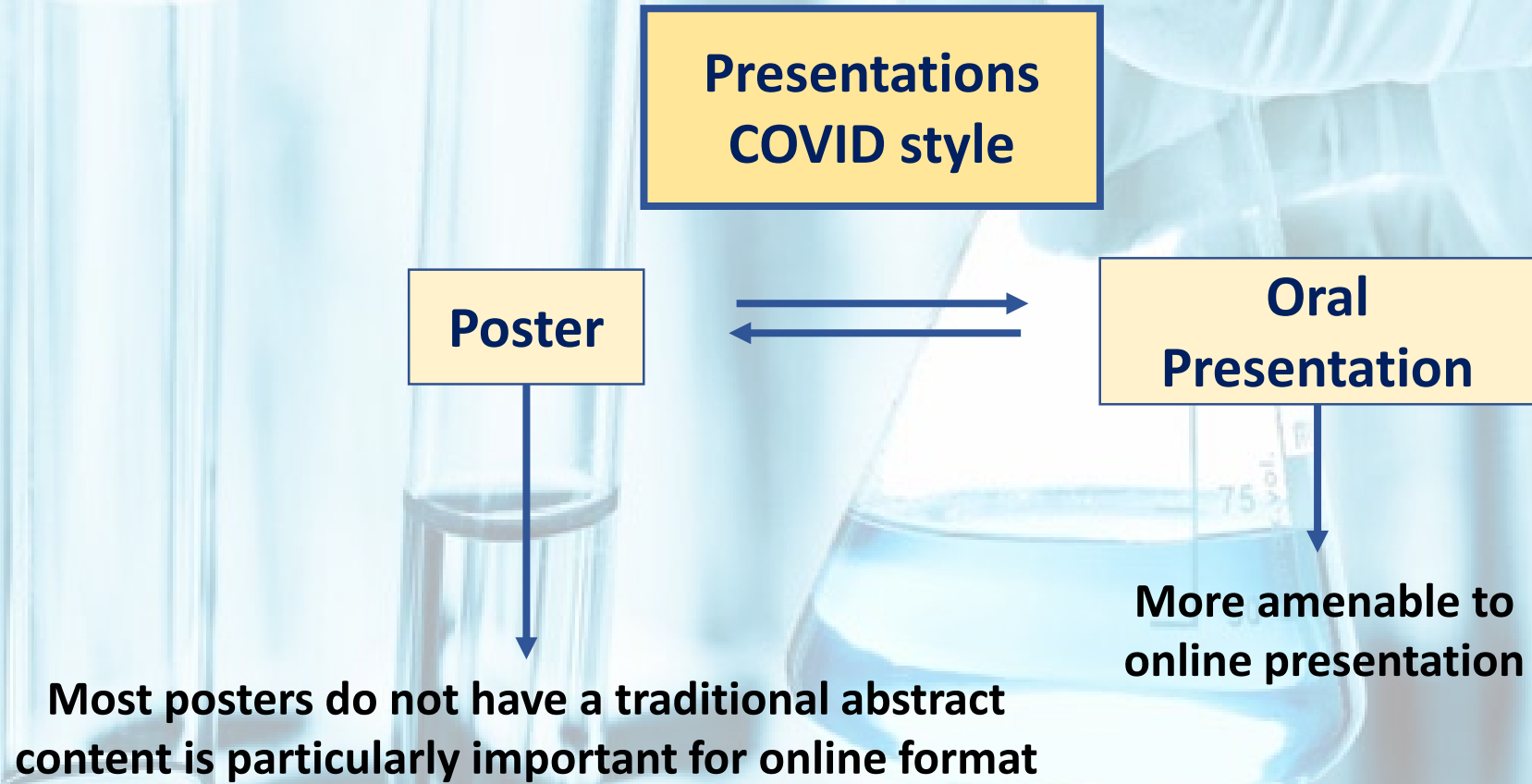
**Research Team**



**Retrospective  
Prospective  
One visit  
Survey  
Longitudinal  
Fluid Collection &  
Measures  
Multiple Measures  
Equipment**



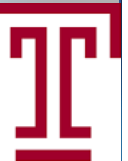
# From Research to Write-Up



# From Research to Write-Up

**Research  
Idea**

**Presentation,  
Publication  
and BIG \$\$**



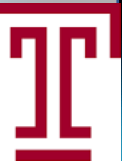
# Posters

---

**Background:** history of progress  
key players in process  
challenges and limitations

**Summary of:** what  
why  
how  
where  
who  
outcome  
next steps

Making the POSTER: Want to create as a map for the reader that clearly leads from one step to the next. Create the poster as if you will not be there to guide audience through it.



## Following Bariatric Surgery

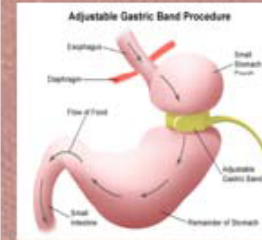
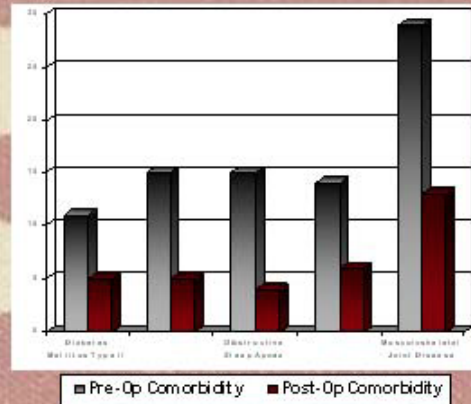
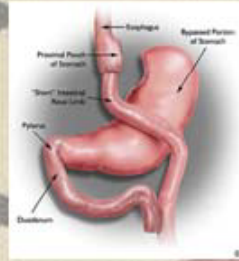
Hamed Abbaszadegan, MD; Melisa Celaya Cortes, MA; Robin Blackstone, MD

Scottsdale Bariatric Center, Scottsdale, AZ

Banner Good Samaritan Medical Center, Department of Internal Medicine, Phoenix, AZ

## Background

Roux-en-Y gastric bypass (RYGB) has been shown to improve health in obese patients. Of note, studies have shown improvements of HbA1c values, insulin resistance, beta-cell function, attenuation of peripheral insulin resistance, improvement of glucose control within 1 month postoperatively, and decrease diabetic medication requirements (1, 2, 3, 4, 5). Factors associated with remission were the preoperative insulin dose and the percentage of excess weight loss (1). One study showed that RYGB improves diabetes resolution by early increase in beta cell function at 1 month, and attenuation of peripheral insulin resistance at 6 months (2).

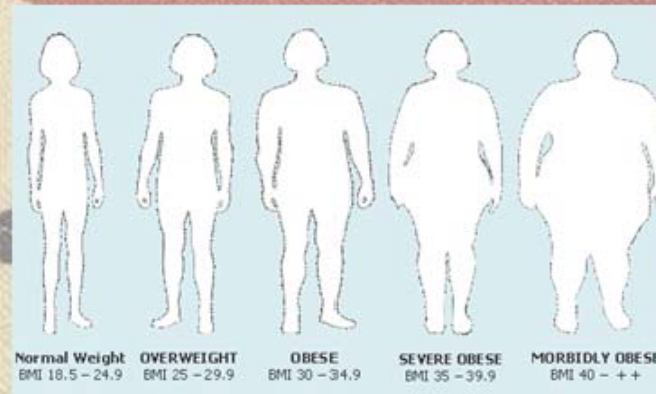


## Results

Among the 29 participants, 86.2% patients are female, median age at surgery is 37.4 years, with the initial consultation median weight at 274 lbs and BMI of 46.5. Preoperative comorbidities include Type II Diabetes (N=11, 37.9%), hypertension (N=15, 51.7%), obstructive sleep apnea (N=15, 51.7%), musculoskeletal joint disease (N=29, 96.6%), and dyslipidemia (N=14, 48.3%). Resolution of comorbidities consists of Type II Diabetes (45.5%) confirmed by serial fasting glucose and HbA1C, hypertension (33.3%) confirmed after PCP stopped HTN medications, obstructive sleep apnea (26.7%) confirmed by repeat sleep study, musculoskeletal joint disease (46.4%) confirmed by subjective history, and dyslipidemia (42.9%) confirmed by fasting lipid panel. A significant difference in percent excess weight loss at 12 months between preoperative Type II Diabetics and normoglycemic patients was not confirmed.

## Introduction

The unique predispositions and prevalence of obesity makes the Native American population a high priority for intervention. Weight loss has been shown in other populations to influence the development and course of diabetes. Recent recommendations by the ADA have suggested that surgery may be an important treatment in the control of diabetes. This study reviews surgical treatment of obesity in a cohort of Native American patients from Arizona including surgical preoperative comorbidities (especially diabetes) and postoperative outcomes.



## Methods

A retrospective analysis of prospectively collected data from November 2001 to November 2008 was performed in Native Americans that underwent gastric bypass (N=22; 75.9%) and laparoscopic adjustable gastric band surgery (N=7; 24.1%) in a community hospital. Descriptive analyses were executed to assess preoperative factors and comorbidities, postoperative complications, and improvement or resolution of disease.

Pre-Operative Comorbidities (Total Patients studied = 29)	Patients with Comorbidities	Percent Resolution of Comorbidities
Diabetes Mellitus Type II	11	45.5%
Hypertension	15	33.3%
Obstructive Sleep Apnea	15	26.7%
Dyslipidemia	14	42.9%
Musculoskeletal Joint Disease	29	46.4%

## Conclusion

The prevalence and severity of obesity and diabetes in Native Americans is amongst the highest in a population group in the world. Post operative comparison with non-Native Americans showed the effects of long term weight loss and resolution of comorbid disease as somewhat less. Unique cultural characteristics may be partly responsible for the lower response rate. Use of gastric bypass and laparoscopic gastric band surgery can aid in achieving long term weight loss and the resolution of comorbid disease.

## References

- Habela, S., Lum, K., Grant, J., Fryer, A., Porterson, D., et al. Resolution of Type 2 Diabetes after Roux-en-Y Gastric Bypass is Associated with Greater Weight Loss. *Surgery for Obesity & Related Diseases*. 2010; 5(2): 205-9.
- Lin, E., Davis, S., Srinivasan, J., Swamy, J., Ziegler, T., et al. Our Mechanism for Type 2 Diabetes Resolution after Roux-en-Y Gastric Bypass. *American Surgeon*. 2008; 75(6):495-502.
- Murphy, D., Mathison, M., Kallies, K., Kothari, S. Effect of Laparoscopic Roux-en-Y Gastric Bypass Surgery on Hemoglobin A1c Levels in Diabetic Patients: a Matched-cohort Analysis. *Surgery for Obesity & Related Diseases*. 2010; 5(7): 4-10.
- Inglis, T., Wiyars, G., Best, J., Henrich, M., Christopoulos, A., et al. Remission of Type 2 Diabetes Mellitus and Improvements in Cardiovascular Risk Factors after Surgical Weight Loss in Adolescents. *Pediatrics*. 2010; 123(1): 214-22.
- Smith, S., Hinojosa, M., Banks, K., Nguyen, N. Remission of Diabetes after Laparoscopic Gastric Bypass. Department of Surgery, University of California Irvine. Presented at the American College of Surgeons in Santa Barbara, CA January 18-20, 2010.



# Cryptogenic Stroke in the Presence of an Atrial Myxoma

Hamed Abbaszadegan, MD; Jeremy Payne, MD, PhD

Banner Good Samaritan Medical Center | Department of Internal Medicine, Phoenix, AZ

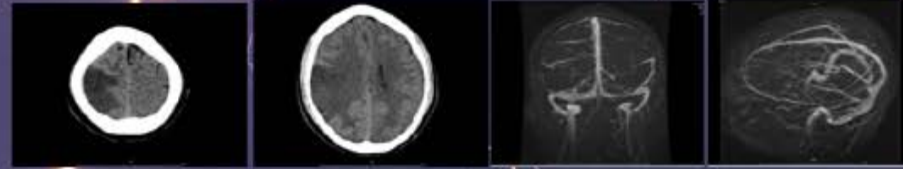
## Introduction:

Strokes are often thought of as an occurrence in patients with risk factors such as long-standing hypertension, hypercholesterolemia, diabetes mellitus, "older" age, smoking, and genetic factors to name a few. It is not as common to see strokes in the younger age population (less than 40 years old), especially in the absence of cardiac/brain anomalies, right to left shunting, trauma, or endocarditis. When stroke occurs in this age group, the work up is often exhaustive to exclude clotting disorders, autoimmune conditions, and structural defects.

## Case Report:

The patient is a 32 year old African American male with no known PMH who presented to the hospital with sudden onset of mild headache, left-sided weakness, and left spatial neglect. During the patient's admission, it was determined that he had an acute right parietal lobe ischemic infarct. Extensive work up did not find a definitive cause, but a right atrial myxoma was incidentally found. There was no clearly visualized patent foramen ovale, however a bubble study suggested a small degree of right to left shunting. No vascular anomaly on MRA imaging was found. Extensive lab work up which included coagulation studies, comprehensive drug screening, cultures, autoimmune etiologies, and lipid studies was unremarkable. The patient was discharged to acute rehab with a potentially cryptogenic stroke. Follow up is to include a repeat transesophageal echo to confirm the myxoma is still present which would then require surgical evaluation for excision.

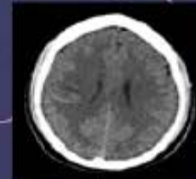
## Initial CT & MRA



## 2<sup>nd</sup> CT



## 3<sup>rd</sup> CT, Day 9



## Risk Factors for Ischemic Stroke Age 15-49



## Transesophageal Echocardiogram



## Discussion:

Often co-morbid disease, drug use, smoking, and other high risk activities can predispose patients to pro-thrombotic events. This was not the case in our patient. Etiologies to rule out before tagging a patient with a "cryptogenic" title should include: structural anomalies of the brain (CT + MR imaging), lipid profile, coagulation studies (factor V Leiden mutation, anti-thrombin III, lupus anticoagulant, cardiolipin, prothrombotic gene mutations, homocysteine), infectious etiologies, and auto-immune etiologies (Anti-nuclear antibody, rheumatoid factor). An embolic particle no larger than 1mm is sufficient to cause a clinically significant stroke. Despite no definitive R→L shunt, it is not impossible to imagine a small piece of the myxoma dislodging from an unseen small shunt.

•Annual Stroke rate for ages 15-49 = 10.0/100,000

- References:
1. Kizer, Jorge. Evaluation of the Patient with Unexplained Stroke. *Coronary Artery Disease*. 2008; 19(7): 335-40.
  2. Putzala, J, Meliso, A, Meliso, T, et. al. Analysis of 1000 Consecutive Patients Aged 15 to 49 With First-Ever Ischemic Stroke. *Stroke*. 2003; 40:1135-1203.

Replace with logo

# Team Approach to Palliation: Do No Harm!

Replace with logo

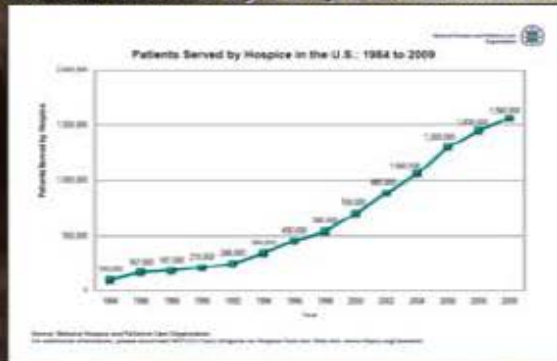
Hamed Abbaszadegan, MD; Mona Amini, MD; Masood Kisana, MD  
Banner Good Samaritan Medical Center/Carl T. Hayden Veterans Affairs Medical Center

## Introduction

Palliation involves easing the severity of pain, non-pain physical symptoms, and improving overall quality of life when the disease process cannot be reversed. The fine line between knowing when to allow natural death, and when to continue aggressive interventions is often skewed. The palliative care team at the Phoenix VA Medical Center has vastly changed the approach to end of life care utilization in the last year by improving utilization by 71%.

High health care expenses are utilized during the last year of life and are found to be mostly incurred in the last month of life. The utilization of palliative medicine is an important topic not just regarding health care expense, but is also significant when discussing patient safety when interventions will not change the

## Patients Served by Hospice: 1984 to 2009



## References

## Health Care (per capita) Cost Inversely Correlated with Quality of Life Score



Figure. Association between cost and quality of death in the final week of life (adjusted  $P = .006$ ). Age, sex, education status, survival time, race/ethnicity, and source of report were controlled for in the adjusted analysis of per capita cost predicting quality of death in the deceased cohort ( $n = 315$ ).

Wong J, Zhang B, Singh A, Furlong H, Brown M, Hays RD. Health Care Costs and Quality of Death in the Final Week of Life. *JAMA Intern Med.* 2010;170(10):933-939.

## Case Report

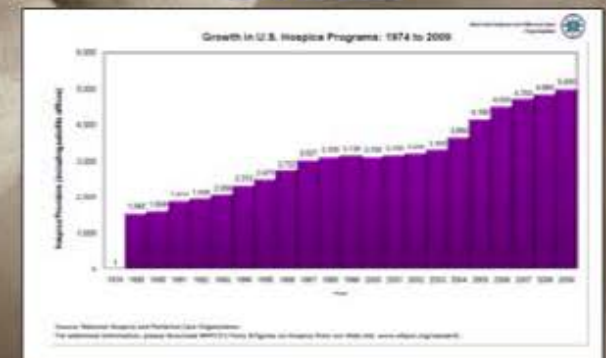
Patient is a 66 y/o Male with a 3 month history of progressive dysphagia to solids/liquids, and an associated significant weight loss. He was diagnosed with a metastatic esophageal adenocarcinoma with diffuse bony metastases confirmed by PET imaging. His symptom control became unmanageable at home secondary to recurrent hematemesis, fatigue, and anorexia to a point where a decision had to be made between aggressive interventions and allowing for natural death with dignity and comfort. Goals were established to control symptoms as a priority, as the metastatic cancer could not be reversed. By providing optimal pain relief, and relief of non-pain physical symptoms, aggressive agonizing interventions were avoided.

## Conclusion

Terminal illness cannot be reversed. Once functional status declines to a point of irreversibility, palliation is an appropriate option for patient safety. Utilization through early involvement of palliative care improves quality of life, leads to less aggressive care, and results in longer survival. Research has shown that palliative medicine interventions not only improve survival, but are more effective than active treatment in many situations.

Advanced heart failure with recurrent exacerbations, advanced COPD, as well as cancers should be considered for palliation approaches as symptom management becomes the forefront of care. Families are often most satisfied with the care when they know their loved one has not been allowed to suffer needlessly.

## Growth of Hospice Programs in U.S. 1974 to 2009



## Introduction

Glossopharyngeal neuralgia (GPN) is a rare disorder of the ninth cranial nerve in which paroxysms of severe pain are associated with excessive vagal outflow. This can result in bradycardia, hypotension, syncope and even cardiac arrest. This is likely mediated by the branch off the glossopharyngeal nerve that supplies the carotid body and carotid sinus which conveys chemoreceptor and baroreceptor information. This mechanism is responsible for the arrhythmogenicity and vasoplegia. Causes include neoplasm, infection, vascular malformations, Eagle's syndrome and prior surgical interventions. We present a case of GPN which resolved with treatment of a head and neck cancer.

## Case Presentation

A 71-year-old male presented with left sided headaches and symptomatic bradycardia three months following diagnosis of squamous cell carcinoma (SCC) of unknown primary with bulky left cervical adenopathy. He described a constant dull left sided headache with paroxysms of sharp, stabbing, and shooting pain lasting seconds at a time. The paroxysms were associated with hiccups, anxiety, an impending sense of doom, bradycardia to the 40s, and hypotension to 50s/30s. To stabilize his autonomic symptoms, he required intravenous atropine pushes and a dopamine infusion. A temporary pacemaker was placed. Imaging revealed progression of his left cervical tumor. It measured 3.4cm x4.4cm x 5.1cm with infiltration into the parotid gland and parapharyngeal space. This caused compression of the carotid artery near the carotid sinus branch of the glossopharyngeal nerve. He was also found to have cerebral vein thrombosis.



EKG: HR 35, PR 126, QRS 100, QTc 396. Marked bradycardia.

## Glossopharyngeal Neuralgia

Glossopharyngeal neuralgia (GPN) was first described in 1910 by Weisenburg and the term "glossopharyngeal neuralgia" was coined in 1921 by Harris. The first case of cardiac arrest and syncope associated with GPN was published in 1942 by Wortis *et al.* This is a rare craniofacial pain syndrome. Katusic published a 39-year retrospective study (1945-1984) calculated an incidence of 0.7/100,000 population/year. And syncope is even less common. In 1981 Rushton *et al.* reported 217 patients admitted to the Mayo Clinic with GPN. Only two patients experienced syncopal events.

Syncope is a result of extreme bradycardia and even asystole preceded by intermittent lancinating pain in the oropharynx, retropharyngeal space and occipital-temporal region with occasional radiation to the ear. The mechanism is not fully understood but the close connection of the vagus and glossopharyngeal nerve is presumed to create a vasoglossopharyngeal reflex arc whereby pain triggers arrhythmogenicity and vasoplegia. Thus, pain can activate the reflex and result in syncope.

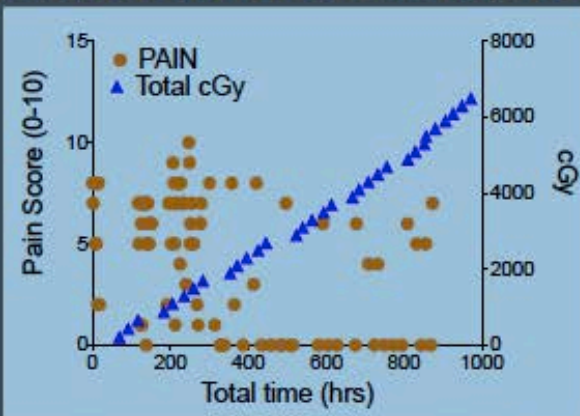


Figure 1 Decrease in reported pain scores over time with increasing radiation represented in cumulative centiGray (cGy).

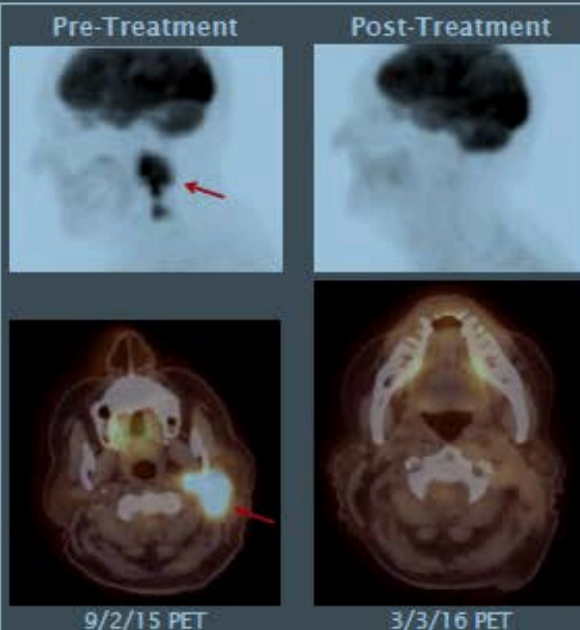
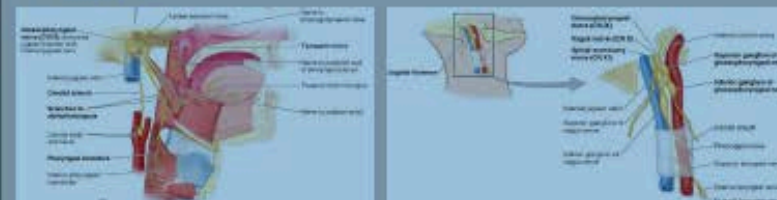


Figure 2 PET before (left) and 6-months after (right) treatment with chemoradiation. Red arrow points to tumor.

## Glossopharyngeal Nerve

The glossopharyngeal nerve is the ninth cranial nerve (CN IX). It emerges from the medulla and traverses the cranium through the jugular foramen with the vagus nerve (CN X) and the spinal accessory nerve (CN XI). It has several components and functions:

- Somatic Motor: motor to stylopharyngeus for swallowing
- Visceral Motor: parasympathetic innervation to the parotid gland
- Special Sensory: visceral sensation from the parotid gland, carotid body and sinus, pharynx and middle ear
  - Carotid body and sinus (Nerve of Hering): chemoreceptor and baroreceptor
- Somatic Sensory: taste to the posterior third of the tongue and cutaneous sensation from external ear



Glossopharyngeal nerve (CN IX) anatomy. Adopted from Clinically Oriented Anatomy for Review.

## Therapy and Resolution

There is no standard treatment for GPN due to the variety of causes. Case reports describe improvement with medical therapy alone with antiepileptics such as carbamazepine, gabapentin and amitriptyline. Other reports show improvement with microvascular decompression surgically or with stereotactic radiosurgery. Given our patient's bulky, invasive, Stage IVa (T<sub>4</sub>N<sub>2</sub>bM<sub>0</sub>) p16+ SCC, he was treated with chemotherapy and radiation in conjunction with neuromodulating medications. He completed thirty-two radiation treatments to a cumulative dose of 65Gy concurrently with cisplatin. This decreased the size of the mass as seen in Figure 2. His pain and hemodynamic symptoms improved with therapy. He self reported lower pain scores with increasing cumulative Gray as seen in Figure 1. With improvement in symptoms of pain and syncope, the temporary pacemaker was removed, and he was transitioned to maintenance therapy with gabapentin. In this instance, he achieved sustained resolution of GPN and its hemodynamic consequences with chemotherapy and radiation to his left cervical mass.

## Conclusion

This case displays how a large squamous cell carcinoma resulted in a painful syncopal phenomenon called glossopharyngeal neuralgia. It also reveals how chemotherapy and radiation produced symptomatic relief. While this is a rare entity, it is worthwhile for both general practitioners and subspecialists to draw a connection between facial pain syndromes and syncope as it may prevent life threatening complications.



# Hidden in Plain Sight: False Reassurances Obscuring a Case of Intravascular Lymphoma

Jeffrey Bien, MD<sup>1</sup>; Renee Honeyfield, MD; Jonathan Pak, MD  
Department of Medicine, Oregon Health & Science University, Portland, OR



VA HEALTH CARE  
Defining EXCELLENCE in the 21st Century

## Introduction

An ill 67 year old man presents with weakness and profound failure to thrive immediately following an episode of syncope.

## Background

- For the preceding 6 months, he has been undergoing an exhaustive workup for chronically progressive B-symptoms and elevated inflammatory markers, including ferritin 1600 ng/mL, CRP 18 mg/L, ESR 94 mm/hr, and LDH 300U/L without hemolysis.
- Wife additionally describes 1 year of “personality changes” including sudden anger, anxiety, and extremely vivid dreams – all new.
- Thought to have polymyalgia rheumatica, he received escalating doses of prednisone, up to 60mg daily for over a month, which briefly improved symptoms though were stopped given transient efficacy and development of significant anasarca, transudative pleural effusion, pericardial effusion, and progressive weakness.
- Over the 2 months preceding admission, he experienced progressively worsening dyspnea, weakness, and dysphonia against a background of a more gradual decline in renal function and persistent sinus tachycardia without a satisfactory diagnosis.
- Outpatient workup includes:
  - negative ANA, ANCA, RF, PPD, viral hepatitis, HIV, Lyme testing
  - SPEP, UPEP, IgG, IgA, and iron studies within normal limits
  - reassuring CT Chest, Abdomen, Pelvis (mild splenomegaly)
  - normal bone marrow biopsy
  - PFTs notable for obstructive disease with low DLCO
- Unremarkable past medical history, family history, medications
- Social history: Accomplished jazz saxophonist, working “up until a few weeks ago”. No cigarettes or alcohol since age 27. No IVDU.

## Presentation

- Reports syncope while walking slowly after 1 day of acute on chronic dyspnea in setting of a week of worsened fatigue, lack of appetite, dysphonia, and profound weakness.
- Review of Systems: Continued B-symptoms. No chest pain, palpitations, cough, urinary symptoms, diarrhea, vomiting, or evidence of bleeding.
- Vitals/Exam: afebrile, HR 111, BP 81/50, RR 26, O2 93% on room air. Thin white male, no acute distress, mildly confused though otherwise neurologically intact, dry mucous membranes, irregularly irregular tachycardia, decreased left base breath sounds with normal work of breathing, 3+ lower extremity edema to mid back.
- Pertinent Labs: Hb 7.1, MCV 74, WBC 6.8, platelets 168, Na 126, Cr 1.7, CK 2, Albumin 1, and lactate 5.5 which improves with crystalloids. CRP 18, ESR 140, LDH 287

## Hospital Course and Transfer

- Initially admitted to the ICU, presumptively treated for septic shock, adrenal insufficiency, and anemia with antibiotics, 2g methylprednisolone IV daily and blood transfusions for several days without clinical or diagnostic progress.
- Consideration for insidious malignancy such as intravascular lymphoma entertained, but ruled out due to normal peripheral blood flow cytometry and cytogenetics (along with recent normal bone marrow biopsy).
- Transferred to tertiary care center for continued workup and care.
- Upon arrival, noted to be mildly tachycardic and tachypneic though saturating 100% on room air. Recommendations placed for further imaging, labs, and studies including a skin and fat pad biopsy.
- However, within 24 hours of arrival patient suddenly began gasping for air with rapidly deteriorating bradycardia. He was found to be in PEA arrest and unfortunately died.
- Autopsy confirmed diffuse organ involvement of intravascular diffuse large B-cell lymphoma.
- Immediate cause of respiratory arrest attributed to “severe leukostasis” of “alveolar capillaries congested with neoplastic cells”.

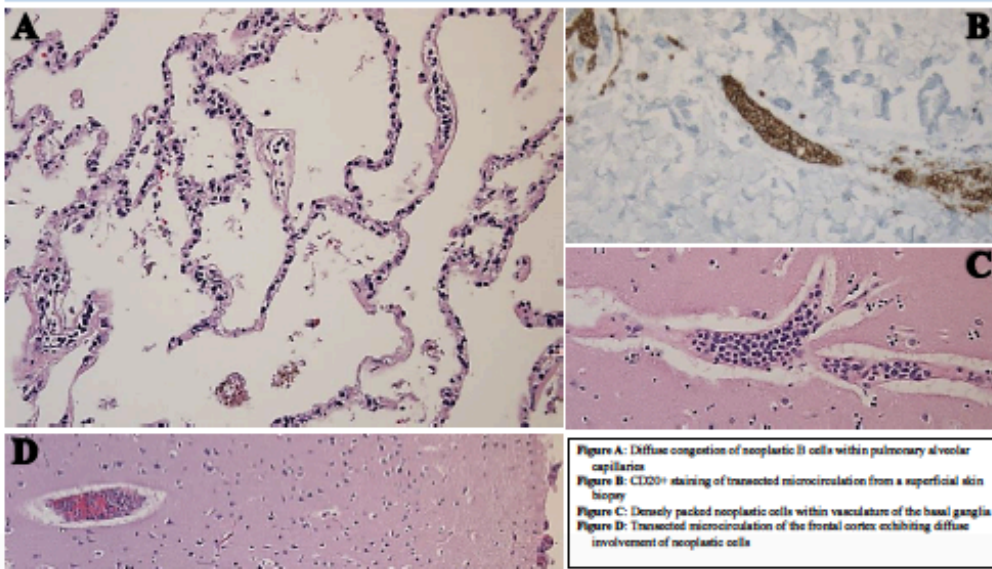
## Extent of Organ Involvement

Specifically noted on pathologic examination to involve microcirculation of the following organs:

- Lung (fig. A)
- Aortic vasa vasorum
- Thyroid
- Kidney
- Prostate
- Stomach
- Spleen
- Skin (fig. B)
- Central Nervous System:
  - Basal ganglia (fig. C)
  - R. frontal (fig. D) & occipital cerebral cortex
  - Pituitary gland (anterior and posterior)
  - Choroid plexus of medulla
  - Thalamus

Note: NOT seen in bone marrow or lymph nodes

## Pathologic Findings



## Discussion

- Intravascular lymphoma is an extremely rare subtype of extranodal diffuse large B-cell lymphoma characterized by tumor proliferation within the lumina of small blood vessels.<sup>1</sup>
- The entity was first described in 1959 as “angioendotheliomatosis proliferans systemisata” by Pfleger and Tappeiner, who theorized the malignancy derived from the endothelial cells themselves.<sup>2</sup>
- Given its rarity and nonspecificity of symptoms, diagnosis is difficult: over 60% of cases involving CNS are diagnosed postmortem.<sup>3</sup>
- Only 5-9% of cases of intravascular lymphoma are detectable in peripheral blood.<sup>1</sup> Small studies point to aberrant expression of markers which home to endothelial cell surface ligands, or aberrant lymphocyte homing and transvascular migration signaling.<sup>4,5</sup>
- Therefore, a random skin biopsy is the diagnostic test of choice.<sup>6,7,8</sup>
- In this case, presence of intravascular lymphoma was in fact suspected at the referring hospital, though prematurely ruled out given normal bone marrow negative peripheral cytogenetics and peripheral flow cytometry. Nevertheless, disease involvement was clear on postmortem skin biopsy.
- This case illustrates key characteristics that can increase suspicion:<sup>9</sup>

	Anemia	↑LDH; B <sub>2</sub> -microglobulin	↑PESR	Hepatic/renal/thyroid dysfunction
Incidence	65%	80-90%	43%	15-20%

- The literature further describes two distinct phenotypes: Western and Asian, which vary in organ involvement.<sup>9</sup> Interestingly, this case transcends the International Consensus Guidelines:

	CNS	Skin	Bone Marrow	Liver, spleen
Western	+	+		
Asian			+	+

- Early-diagnosed cases have been successfully treated with aggressive chemotherapy such as R-CHOP.<sup>1</sup>

## Teaching Points

- Symptoms of intravascular lymphoma are nonspecific, though the presence of an inexplicable inflammatory state, elevated LDH, anemia, and organ dysfunction can raise suspicion.
- Definitive diagnosis is made via random skin biopsy.
- Distinction between Asian and Western phenotypes are not clear-cut.

## References

1. Zuckerman D, Salles M, Houlding R. Intravascular Lymphoma: The Oncologist's “Great Imitator”. *The Oncologist* 2006;11(2):494-502. doi:10.1200/JCO.2005.11.0-494.
2. Pfleger G, Tappeiner T. On the morphology of lymphomatous endotheliomatosis of the intravascular blood vessels (angioendotheliomatosis). *Revue* 1959;10:339-345.
3. Finkels R, Luk R, Salles M, Chinnai S, Wang ET. The natural history of intravascular lymphomas. *Cancer Med* 2014;3(9):1001-1004. doi:10.1089/cam.2014.0040
4. Kasai H, Kuroki T, Okabe S, Tamura S, Kobayashi M. Intravascular large cell lymphoma: histopathological, immunohistochemical and molecular genetic study. *Leuk Lymphoma* 1999;34(7-8):949-958. doi:10.1080/10420159910885028481
5. Pimentel M, Angelini D, Chinnai S, et al. Lack of CD20<sup>+</sup> (anti-lymphoma) and CD19<sup>+</sup> (anti-B-cell) antibodies in intravascular lymphomas. *Ann Pathol* 2005;25(2):252-255.
6. Ando N, Okamura J, Okuma S, et al. Use of random skin biopsy for diagnosis of intravascular large B-cell lymphoma. *Alzheimers Dis Prev* 2007;10(2):102-107.
7. Caspi A, Radtke M, Tappiner M. Early diagnosis of intravascular large B-cell lymphoma showing intravascular lymphoma by random skin biopsy. *J Geriatr Oncol* 2009;20(7):771-774. doi:10.1215/08980101-000001274
8. Maitani S, Kasai H, Chinnai S, et al. Random skin biopsy and bone marrow biopsy for diagnosis of intravascular large B-cell lymphoma. *Ann Hematol* 2011;90(4):747-751. doi:10.1007/s00277-010-1011-9
9. Pimentel M, Pined A, Lopez E, et al. Definition, diagnosis, and management of intravascular large B-cell lymphoma: Proposal and Perspective From an International Consensus Meeting. *JCO* 2007;25(1):148-157. doi:10.1200/JCO.2006.08.2613

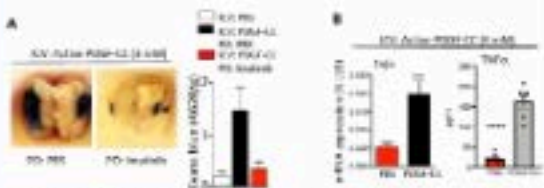
# Blocking PDGF-CC signalling ameliorates multiple sclerosis-like neuroinflammation by inhibiting disruption of the blood-brain barrier

M. ZEITELHOFFER<sup>1</sup>, M.Z. ADZEMOVIC<sup>2</sup>, C. MOESSINGER<sup>1</sup>, C. STEFANITSCH<sup>1</sup>, C. STRELL<sup>3</sup>, L. MUHL<sup>1</sup>, L. FREDRIKSSON<sup>1</sup>, T. OLSSON<sup>2</sup>, U. ERIKSSON<sup>1</sup> and I. NILSSON<sup>1</sup>

<sup>1</sup>Vascular Biology division, Dept. Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden; <sup>2</sup>Neuroimmunology unit, Dept. Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; <sup>3</sup>Dept. Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden

## INTRODUCTION

- Multiple sclerosis (MS) is an inflammatory demyelinating disease characterized by loss of blood-brain barrier (BBB) integrity and infiltration of immune cells into the CNS.
- Development of novel treatments for MS, preferably acting on molecular targets expressed exclusively at the BBB and not on immune cells, should decrease the risk for adverse complications.
- Activation of platelet-derived growth factor-C (PDGF-CC) signaling via PDGF $\alpha$  in CNS regulates BBB opening and inhibition of this pathway can be accomplished using the small tyrosine kinase inhibitor imatinib.



**Figure 1. PDGF-CC signaling promotes BBB opening and induction of pro-inflammatory cytokines.**  
A) Intracerebral injection (ICJ) of IgG (BBB opening) or PDGF-CC leads to opening of the BBB and vascular leakage within 7 h as measured by IgG extravasation. The small PDGF-CC treatment with neutralizing antibody (anti-PDGF-CC) prevents PDGF-CC induced vascular leakage.  
B) IgG extravasation and TNF- $\alpha$  protein expression is induced after PDGF-CC ICJ in progression pathology in endothelial cells and pericytes. In a pro-inflammatory BBB of mice. Transmembrane proteins mediating endothelial cell-cell and cell-matrix interactions (tight junctions) are highly regulated in EAE. ICJ of IgG and protein levels mediated by ROS in ECs collected at 8 h post-ICJ (open circles).

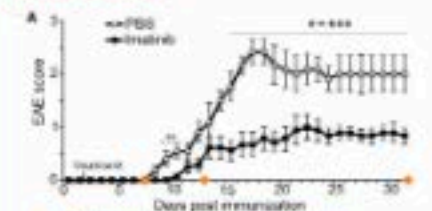
## AIM

- To study BBB phenotypic and transcriptional changes during experimental autoimmune encephalomyelitis (EAE) in mice, as this will increase the understanding of molecular mechanisms controlling BBB function and integrity in health and disease, a prerequisite for developing novel therapeutic strategies.

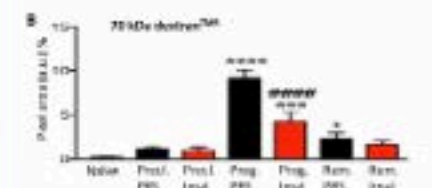
## METHOD

- Systematic profiling of transcriptional and phenotypic changes at the BBB during multiple sclerosis-like progression (MS)-induced experimental autoimmune encephalomyelitis (EAE) in mice.
  - Work from endothelial cell and pericyte lineages from spinal cord represent the BBB in progression and was further identified (Adzemic et al., Nat. Rev. 2013).
  - Genes from the Affymetrix Gene 2.0 ST array that met  $n = 2$  fold (2) fold change cut-off and an adjusted P value < 0.05 were up-loaded in the Ingenuity pathway analysis software.
- 

## RESULTS



Time points of vascular target inhibition: **Naive** (Pre-EAE), **Preclinical** (Pre-EAE), **Progression** (EAE), **Remission** (EAE).

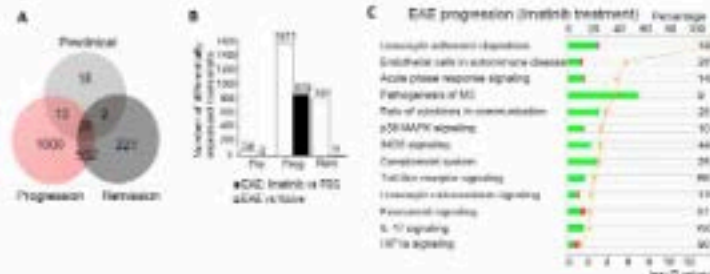


**Figure 2. Neurological scoring and assessment of BBB integrity during EAE reveal three demyelinating disease phases: preclinical, progression and remission.**

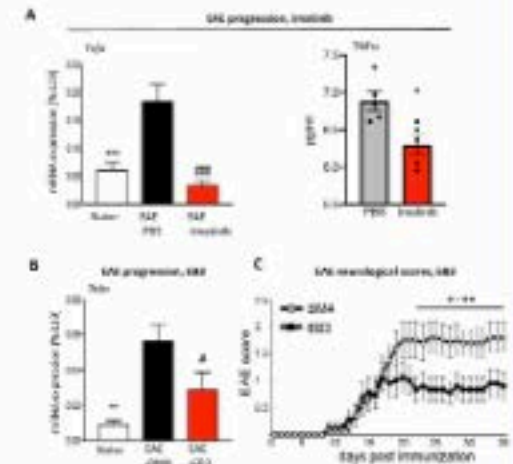
- Neurological scoring during EAE according to 0-4 neurological scores of EAE in tail palpation, 2-rod gait, posture in hindlimbs, 2-rod gait analysis or paraparesis and/or paraplegia in hindlimbs. Pre- and imatinib treatment (200 mg/kg/day) delay onset and ameliorates neurological symptoms during progression.
- Quantified integrity of the BBB assessed in vivo using a circulating dextran<sup>70</sup> (DX-70). Quantification reveals dramatic leakage of 70 kDa dextran<sup>70</sup> in the preclinical phase, massive leakage in the progression phase and closing of the BBB again in mice for the remission phase. BBB-leakage at progression phase effectively inhibited by imatinib.

## CONCLUSIONS

- Dynamic transcriptional and phenotypic changes occur at the BBB during experimental autoimmune encephalomyelitis (EAE) in mice
- Both imatinib and a selective neutralising anti-PDGF-CC antibody counteract phenotypic and transcriptional changes at the BBB, correlating with amelioration of EAE



**Figure 3. KEGG pathway analysis of the BBB transcriptional changes in EAE: Impact of imatinib.**  
A) Venn-diagram showing the number of differentially expressed genes in the BBB transcriptional changes and the overlap in the different phases of EAE. The unique DEGs in progression, remission and both phases are shown. The overlap in the different phases is shown in orange for all three disease phases.  
B) The BBB gene expression profile of the pre-demyelinating, i.e. naive to myelination of blood vessels is characterized by upregulation of transcriptional regulators of endothelial cell activation (EPCs, ECs), lipid and leukocyte adhesion (LeucA), TNF $\alpha$  as well as activation of chemokines (CXCL1 and CXCL2). In the progression phase, 5 pathways related to leukocyte adhesion and endothelial cell activation were affected (IL12, MIF, MIFR, MIFR2, MIFR3, MIFR4, MIFR5, MIFR6, MIFR7, MIFR8, MIFR9, MIFR10, MIFR11, MIFR12, MIFR13, MIFR14, MIFR15, MIFR16, MIFR17, MIFR18, MIFR19, MIFR20, MIFR21, MIFR22, MIFR23, MIFR24, MIFR25, MIFR26, MIFR27, MIFR28, MIFR29, MIFR30, MIFR31, MIFR32, MIFR33, MIFR34, MIFR35, MIFR36, MIFR37, MIFR38, MIFR39, MIFR40, MIFR41, MIFR42, MIFR43, MIFR44, MIFR45, MIFR46, MIFR47, MIFR48, MIFR49, MIFR50, MIFR51, MIFR52, MIFR53, MIFR54, MIFR55, MIFR56, MIFR57, MIFR58, MIFR59, MIFR60, MIFR61, MIFR62, MIFR63, MIFR64, MIFR65, MIFR66, MIFR67, MIFR68, MIFR69, MIFR70, MIFR71, MIFR72, MIFR73, MIFR74, MIFR75, MIFR76, MIFR77, MIFR78, MIFR79, MIFR80, MIFR81, MIFR82, MIFR83, MIFR84, MIFR85, MIFR86, MIFR87, MIFR88, MIFR89, MIFR90, MIFR91, MIFR92, MIFR93, MIFR94, MIFR95, MIFR96, MIFR97, MIFR98, MIFR99, MIFR100).  
C) The BBB transcriptional changes in EAE induced mice treated with the neutralizing anti-PDGF-CC antibody (Imat) show a similar effect on the TNF $\alpha$  regulatory profile as imatinib.  
D) Neurological scoring during EAE reveals amelioration of clinical symptoms with anti-PDGF-CC treatment (Imat) compared to control (IgG) (anti-PDGF-CC treated) mice.



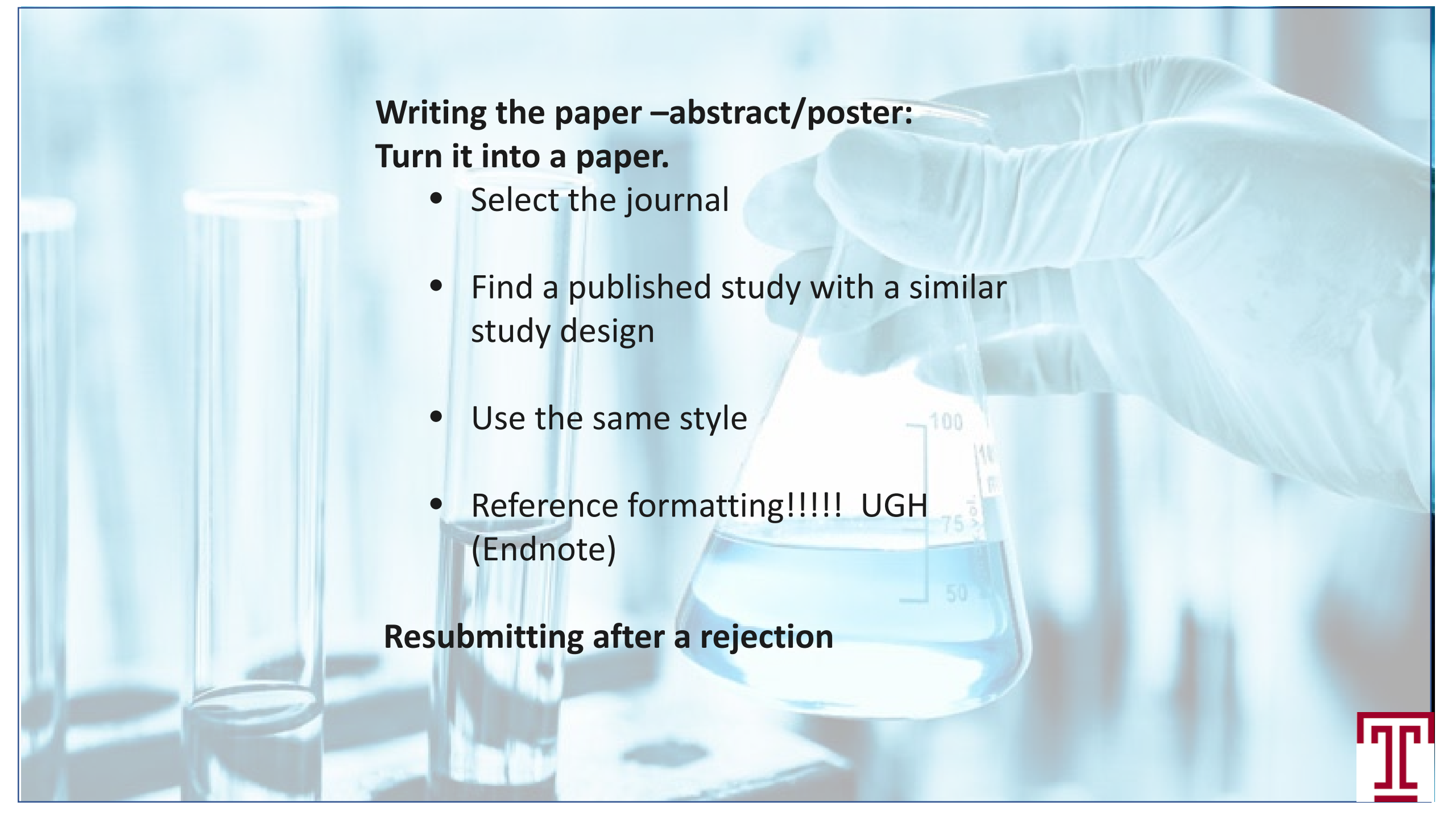
**Figure 4. Specific targeting of PDGF-CC using IgG antibody phenocopies imatinib.**  
A) EAE-induced disruption of the BBB is effectively inhibited (left panel). TNF $\alpha$  protein levels in CSF are significantly decreased by imatinib (right panel).  
B) The BBB transcriptional changes in EAE induced mice treated with the neutralizing anti-PDGF-CC antibody (Imat) show a similar effect on the TNF $\alpha$  regulatory profile as imatinib.  
C) Neurological scoring during EAE reveals amelioration of clinical symptoms with anti-PDGF-CC treatment (Imat) compared to control (IgG) (anti-PDGF-CC treated) mice.

## REFERENCES

- Zeitelhofer M, Adzemic MZ, Moessinger C, Stefanitsch C, Strell C, Mühl L, Fredriksson L, Olsson T, Eriksson U and Nilsson I (2020) Imatinib ameliorates neuroinflammation in a rat model of multiple sclerosis by enhancing blood-brain barrier integrity and by modulating the peripheral immune response. *PLoS One* 2020;15(2):e0229886.
- Lawandowski SA, Jankovic J, Fredriksson L, Larsson B, Mühl L, Zeitelhofer M, et al. Phosphorylation activation of the PDGF-CC pathway accelerates onset of ALS neurodegeneration. *Acta Neuropathol*. 2020;131(3):453-64.
- Adzemic MZ, Nilsson I, Lawandowski SA, Kpfi J, Codolazzi S, Olsson T, et al. Imatinib enhances functional recovery after spinal cord injury. *PLoS One* 2013;7(4):e52760.

## CONTACT INFORMATION

**Ingrid Nilsson**, PhD, Senior Researcher  
Division of Vascular Biology  
Department of Medical Biochemistry and Biophysics  
  
Karolinska Institutet  
E-mail: ingrid.nilsson@ki.se  
web: www.mbb.ki.se



**Writing the paper –abstract/poster:  
Turn it into a paper.**

- Select the journal
- Find a published study with a similar study design
- Use the same style
- Reference formatting!!!! UGH  
(Endnote)

**Resubmitting after a rejection**

# Abstracts

**Disease/Disorder Topic**

**Significance and Knowledge Gap**

**Population/Cohort Studied**

**Research Setting (hospital/clinic)**

**Materials, Methods and Analyses**

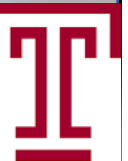
**Outcome/Results**

**How findings improve health care/QOL**

**Next step based on these results**

**Space  
Constraints  
Word Count**

**Specific  
Format**





The NEW ENGLAND  
JOURNAL of MEDICINE

<https://www.nejm.org/author-center/article-types>  
<https://www.nejm.org/author-center/article-types>







## References managers

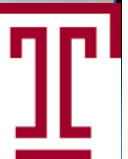
---

Endnote\*

Edit

Output Styles

*NEJM*

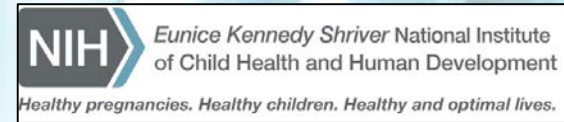


# Find Funding and Write the Proposal

---

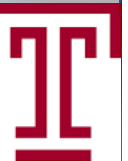
Where to look??

NIH



Foundations

Professional Societies



# Writing an NIH grant proposal

---

**Start with a example of a proposal of the same series (R21, R01, etc)!**

**Work with your Administrator!**



# Most Difficult Part

---

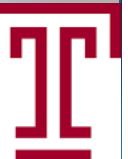
**Where to look??**

**NIH**

**Institute?** <https://www.nih.gov/institutes-nih/list-nih-institutes-centers-offices>

**Series?** <https://researchtraining.nih.gov/programs/career-development>

**ASK FOR HELP!**



A hand wearing a white nitrile glove holds a glass flask containing a blue liquid. The flask has volume markings for 50 and 75. In the background, several test tubes are visible on a lab bench. The entire scene is overlaid with a semi-transparent blue filter. Two horizontal blue lines are positioned above and below the text.

# Questions and Moving Forward

