

Biographical Sketch

Principal Investigator/Program Director (Last, First, Middle): ORAL, ELIF ARIOGLU

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Elif Arioglu Oral, M.D.	POSITION TITLE Assistant Professor of Medicine		
eRA COMMONS USER NAME Eliforal			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Istanbul University, Istanbul, Turkey	M.D.	1986-1992	Medicine

A. Positions and Honors**Positions and Employment**

1993-1994	Intern, Department of Medicine, Sinai Hospital, Detroit, MI
1994-1996	Resident, Department of Medicine, Sinai Hospital, Detroit, MI
1996-1999	Fellow in Endocrinology, Metabolism and Diabetes, Inter-institute Endocrinology Training Program, The National Institutes of Health, Bethesda, MD
1997-1999	Visiting Associate, Diabetes Branch, The National Institute of Diabetes, Digestive and Kidney Diseases, The National Institutes of Health, Bethesda, MD
1999-2002	Senior Fellow, Diabetes Branch, The National Institute of Diabetes, Digestive and Kidney Diseases, The National Institutes of Health, Bethesda, MD
2002-present	Assistant Professor of Medicine, Division of Endocrinology and Metabolism, University of Michigan

Honors

1992	Jaycees, Outstanding Young Persons of Turkey (TOYT) Competition: first place in the category of Medical Innovation
1992	Nomination for the Outstanding Young Persons of the World (TOYP)
1992	Competition organized by Junior Chamber International (JCI) in the same category
1993	Award to the intern/resident best demonstrating excellence in medical research from Sinai Hospital, Department of Medicine 1993/94
1994	Award to the intern/resident best demonstrating excellence in medical research from Sinai Hospital, Department of Medicine 1993/94
1996	Joseph H. Wahlers Award presented by Sinai Hospital to house-staff who most the qualities of kindness, empathy and emotional support of patients
1998	Paper included in Mosby's Yearbook of Medicine (Arioglu E. <i>et al.</i> N Engl J Med 339: 883-86)
1999	Paper included in Mosby's Yearbook of Endocrinology (Arioglu E. <i>et al.</i> N Engl J Med 339: 883-86)

2000-Present Listed in Multiple biography registries
 2005 Selected as the Institutional nominee for Wellcome-Burroughs Foundation
 Translational Researcher Award

B. Research Support

Ongoing Research Support

GCRC Protocol 1995 Oral, EA (PI)
 1/01/04-12/31/06

Grant #M01-RR00042

NASH: Is leptin deficiency an etiological factor? (Phase I)

This study investigates the role of leptin as an etiological factor in the development of nonalcoholic steatohepatitis. The preliminary data presented in this application was obtained partially through support from GCRC.

GCRC Protocol 2145 Oral, EA (PI)
 1/01/07-12/31/09

Grant #M01-RR00042

NASH: Is leptin deficiency an etiological factor? (Phase 2)

This study investigates the role of leptin as an etiological factor in the development of nonalcoholic steatohepatitis. The preliminary data presented in this application was obtained partially through support from GCRC.

Michigan Gastrointestinal Peptide Research Center
 Pilot Feasibility Project Oral, EA (PI)
 9/01/05-8/31/06

Efficacy of leptin for treatment of NASH

This study investigates the role of leptin as an etiological factor in the development of nonalcoholic steatohepatitis. The preliminary data presented in this application was obtained partially through support from GCRC.

GlaxoSmithKline. Oral, EA (PI)
 03/1/05-12/31/06

Effect of Rosiglitazone on Myocardial Blood Flow Regulation in Diabetic Autonomic Neuropathy.

This study investigates potential effects of Rosiglitazone in the amelioration of autonomic function in type 2 diabetic patients.

NIH-NIDDK Conjeevaram H (PI)
 10/01/05-09/30/07

1 R03 DK069913-01

Fenofibrate in the Treatment of NASH.

This pilot study addresses whether there is a therapeutic role for fenofibrate in the treatment of NASH

Role: Co-Investigator

NIH Oral, EA (PI)
 04/01/06-03/31/08

1 R03 DK074488-01

Recombinant leptin therapy for treatment of NASH

This R03 application will test the efficacy of recombinant leptin therapy in patients with NASH and relative leptin deficiency.

Completed Research Support

MDRTC

Oral, EA (PI)

2/01/03-11/30/04

Pilot and Feasibility Grant

Non-alcoholic steatohepatitis: is leptin deficiency a contributing factor?

This study investigates the role of leptin as an etiological factor in the development of nonalcoholic steatohepatitis.

University of Michigan – Internal Award

Oral, EA (PI)

12/01/02-11/30/03

Internal Medicine / Innovative Grants

Evaluation of body composition, metabolic characteristics and leptin levels in nonalcoholic steatohepatitis (NASH).

This study investigates leptin levels and body composition characteristics of individuals with known non-alcoholic steatohepatitis.

University of Michigan – Internal Award

Burant, C (PI)

12/01/02-11/30/03

Internal Medicine / Innovative Grants

Ex-vivo restoration of AGPAT2 expression in skeletal muscle fat cell precursors in patients with generalized congenital lipodystrophy (GCL).

This study evaluates the defects of adipocyte differentiation from the skeletal muscle derived precursor cells of patients with congenital generalized lipodystrophy and seeks to correct these defects by restoration of the mutated AGPAT-2 gene.

Role: Associate Investigator

Selected Publications

- Arioglu E**, Gottlieb NA, Koch CA, Doppman JL, Grey NJ, Gorden P. Natural history of a proinsulin-secreting insulinoma: from symptomatic hypoglycemia to clinical diabetes. *J Clin Endocrinol Metab* 85(10):3628-30, 2000.
- Speckman R, Garg A, Du F, Bennett L, Rose V, **Arioglu E**, Taylor SI, Lovett M, Bowcock AM. Mutational and haplotype analyses in families with familial partial lipodystrophy (Dunnigan variety) reveal recurrent missense mutations in the globular C-terminal domain of Lamin A/C. *Am J Hum Genet* 66(4):1192-8, 2000.
- Chao L, Marcus-Samuels B, Mason MM, Moitra J, Vinson C, **Arioglu E**, Gavrilova O, Reitman ML. Adipose tissue is required for the antidiabetic, but not for the hypolipidemic, effect of thiazolidinediones. *J Clin Invest* 106(10):1221-1228, 2000.
- Reitman ML, **Arioglu E**, Gavrilova O, Taylor SI. Lipoatrophy revisited. *Trends Endocrinol Metab.* 11(10): 410-416, 2000.
- Arioglu E**, Duncan-Morin JL, Sebring N, Rother KI, Gottlieb N, Lieberman J, Herion D, Kleiner D, Reynolds J, Premkumar A, Sumner AE, Reitman M, Gorden, P and Taylor SI. Efficacy and safety of troglitazone in the treatment of lipodystrophy syndromes. *Ann Intern Med*: 133(4): 263-74, 2000.
- Premkumar A, Chow C, Bhandarkar P, Wright V, Koshy N, Taylor SI, **Arioglu E**. Lipoatrophic/Lipodystrophic Syndromes – Spectrum of findings on MR Imaging. *American Journal of Roentgenology* 178: 311-318, 2002.
- Berger JR, **Arioglu Oral E**, Taylor SI. Familial lipodystrophy associated with neurodegeneration and congenital cataracts. *Neurology* 58:43-47, 2002.
- Bolan C, **Arioglu Oral E**, Gorden P, Taylor SI, Leitman SF. Intensive, long-term plasma exchange therapy for severe hypertriglyceridemia in acquired total lipodystrophy. *J Clinical Endocrin and Metab* 87: 380-384, 2002.
- Oral EA**, Simha V, Ruiz, E, Andewelt A, Premkumar A, Snell P, Wagner AJ, DePaoli AM, Reitman M, Gorden P, Garg A. Leptin replacement therapy for lipodystrophy. *New England J Med* 346 (8): 570-8, 2002.
- Arioglu E**, Andewelt A, Diabo C, Bell M, Taylor SI, and Gorden P. Clinical course of the syndrome of autoanti-bodies to the insulin receptor (Type B insulin resistance): a 27-year perspective. *Medicine* 81(2): 87-100, 2002.
- Agarwal AK, **Arioglu E**, de Almeida S, Akkoc N, Taylor SI, Bowcock AB, Barnes RI, Garg A. The gene encoding 1-acylglycerol-3-phosphate O-acyltransferase 2 (AGPAT2) is mutated in congenital generalized lipodystrophy linked to chromosome 9q34. Accepted for publication in *Nat Genet.*; 31(1):21-3, 2002.
- Petersen KF, **Oral EA**, Dufour S, Befroy D, Ariyan C, Yu C, Cline GW, DePaoli AM, Taylor SI, Gorden P, Shulman GI. Leptin reverses insulin resistance in patients with severe lipodystrophy. *J of Clin. Invest.* 109: 1345-1350, 2002.
- Oral EA**, Ruiz E, Andewelt A, Sebring N, Wagner AJ, DePaoli, AM, Gorden P. Effect of leptin replacement on pituitary hormone regulation in severe lipodystrophy. *J Clin Endocrinol Metab.* 87(7):3110-7, 2002.
- Oral EA**. Lipoatrophic diabetes and other related syndromes. *Rev Endocr Metab Disord.* Mar 4(1):61-77 2003.
- Haque WA, **Oral EA**, Dietz K, Bowcock AM, Agarwal AK, Garg A. Risk factors for diabetes in familial partial lipodystrophy, dunnigan variety. *Diabetes Care.* 26(5):1350-5, 2003.
- Simha V, Agarwal AK, **Oral EA**, Fryns JP, Garg A. Genetic and phenotypic heterogeneity in patients with mandibuloacral dysplasia-associated lipodystrophy. *J Clin Endocrinol Metab.* 88(6):2821-4, 2003.

- Agarwal AK, Simha V, **Oral EA**, Moran SA, Gorden P, O'Rahilly S, Zaidi Z, Gurakan F, Arslanian SA, Klar A, Ricker A, White NH, Bindl L, Herbst K, Kennel K, Patel SB, Al-Gazali L, Garg A. Phenotypic and genetic heterogeneity in congenital generalized lipodystrophy. *J Clin Endocrinol Metab.* 2003 88(10):4840-7, 2003.
- Cochran EK, Young JR, Moran SA, DePaoli AM, **Oral EA**, and Gorden P. Efficacy of leptin therapy for the extreme insulin resistance of the Rabson Mendenhall Syndrome. *J Clin Endocrinol Metab.* 89(4):1548-54, 2004.
- Javor E, Moran SA, Young JR, Cochran E, DePaoli AM, **Oral EA**, Turman MA, Blackett JR, Savage D, O'Rahilly S, Balow J and Gorden P. Proteinuric nephropathy in acquired and congenital generalized lipodystrophy: baseline characteristics and course during recombinant leptin therapy. *J Clin Endocrinol Metab.* 89(7):3199-207, 2004.
- Musso C, Cochran E, Moran SA, Skarulis MC, **Oral EA**, Taylor S, Gorden P. Clinical course of genetic diseases of the insulin receptor (Type A and Rabson Mendenhall Syndromes): a 30 year perspective. *Medicine (Baltimore)* 83(4):209-22, 2004.
- Moran SA, Patten N, Young JR, Cochran E, Sebring N, Reynolds J, Premkumar A, DePaoli AM, Skarulis MC, **Oral EA**, Gorden P. Changes in body composition in patients with severe lipodystrophy after leptin replacement therapy. *Metabolism* 53(4):513-9, 2004.
- McDuffie JR, Riggs PA, Calis K, Freedman R, **Oral EA**, DePaoli AM and Yanovski J. Effect of leptin on satiety and satiation in lipodystrophic patients with leptin insufficiency. *J Clin Endocrinol Metab.* 89(9):4258-63, 2004.
- Javor ED, Ghany MG, Cochran EK, **Oral EA**, DePaoli AM, Kleiner DE, Gorden P. Recombinant leptin reverses nonalcoholic steatohepatitis in patients with lipodystrophy. *Hepatology* 41(4):753-60, 2005.
- Van Tits LJH, **Oral EA**, Sweep CGJ, Stalenhoef AFH, Tack CJ. Anti-inflammatory effects of troglitazone in nondiabetic obese subjects independent of changes in insulin sensitivity. *The Netherlands Journal of Medicine* 63(7): 250-255, 2005.
- Oral EA**, Javor E, Cochran E, Ding L, Young JR, DePaoli AM, Holland S and Gorden Phillip. Leptin replacement therapy modulates circulating lymphocyte subsets and T-cell responsiveness in severe lipodystrophy. *Journal of Clinical Endocrinology and Metabolism* 91(2): 621-628, 2006.
- Huang S, Lee L, Hanson NB, Lenaerts C, **Oral EA**, et al. The Spectrum of WRN Mutations in Werner Syndrome Patients. Accepted to *Human Mutation* journal.

Ongoing Clinical Studies and Future Directions

Ongoing Studies:

Nonalcoholic Steatohepatitis: Is Leptin Deficiency an Etiological Factor?
Phase I

Nonalcoholic Steatohepatitis: Is Leptin Deficiency an Etiological Factor?
Phase II

You can also visit the “Engage” Website (<https://www.umengage.org>) under “Find Studies” to see a listing of our studies and to sign up - should you consider participating.

Future Studies:

An Industry-Sponsored Investigational Drug Trial for Treatment of Type II
Diabetes and Severe Insulin Resistance
This drug may have weight loss properties.

Nonalcoholic Steatohepatitis: Is Leptin Deficiency an Etiological Factor? Phase I

Study Purpose:

In this study, we would like to determine the variation in body fat distribution and blood chemistry in patients with fatty liver disease. We also would like to know how these parameters affect the circulating leptin concentrations.

Research Abstract:

Being overweight impairs the action of the insulin hormone, the primary hormone responsible for controlling sugar levels in the body. This is called a state of insulin resistance. Insulin resistance is commonly seen in patients who have fat accumulation in their liver. About 10% of patients with fat accumulation in their liver develop scarring that can lead to failure of liver and death. Another factor that has been shown in research studies to play a role in preventing fat accumulation in the liver is the leptin hormone, a hormone secreted by the fat cells. Previously, we have observed very low leptin hormone concentrations in an unusual group of patients with abnormal body fat. In this group, there was marked fat accumulation and scarring in the liver as well as very severe insulin resistance. Both the liver problem and the insulin resistance remarkably reversed when we administered leptin hormone and achieved near normal leptin levels in these patients for about 4 months. These results made us wonder whether leptin hormone plays a role in the fat accumulation and scarring process in other patients with this condition. However, knowledge about the variation of leptin hormone levels and body composition and how these relate to each other and insulin resistance is lacking. In this study, we would like to determine the variation in body fat distribution and blood chemistry in patients with fatty liver disease. We also would like to know how these parameters affect the circulating leptin concentrations. This study comprises of one day of testing that involves baseline blood work, imaging studies that help to determine body fat distribution and a test that lasts three hours to determine how effective insulin is working in the cells. We will perform these studies on 50 patients with known fat accumulation and scarring. We will use this information to determine if we can develop new therapies to reverse or slow down fat accumulation and scarring in the liver.

Eligibility Criteria:

- ❖ Patients who were found to have nonalcoholic steatohepatitis on their liver biopsy
- ❖ Male patients between the age of 18 and 65
- ❖ We require that all other known causes of liver disease such as viruses and alcohol are excluded
- ❖ We will also exclude patients who have diabetes mellitus and those who are pregnant or lactating
- ❖ Patients with complicated diseases such as kidney or heart failure are ineligible

Principal Investigator/Program Director (Last, First, Middle):

ORAL, ELIF ARIOGLU

Compensation: \$50 per day of participation

The studies in Phase I will only take one day.

If you are interested in participating as a subject in this study, please contact Dr. Oral's study coordinator, Valida Bajrovic, at (734) 615-0539.

Nonalcoholic Steatohepatitis: Is Leptin Deficiency an Etiological Factor? Phase II

Study Purpose:

We would like to see whether restoring leptin levels to normal in eligible patients with fatty liver disease, who have undergone our Phase I study, will improve the disease process in these patients.

Research Abstract:

Nonalcoholic steatohepatitis (or NASH) is known to be caused by deposition of fat in the liver and development of scarring. This condition occurs more frequently in overweight and obese persons. It is often associated with resistance to the actions of insulin hormone. Fat cells secrete a hormone called leptin. Recently, we have learned that obese or overweight persons make too much leptin, which may contribute to insulin resistance. Paradoxically, patients who do not have any fat cells, also have insulin resistance. In these patients, insulin resistance is caused by the absence of leptin and leptin replacement significantly improves insulin resistance and fat deposition in the liver. In an earlier study, we determined the leptin levels in patients with NASH and how these levels are related to body fat levels as well as responsiveness to insulin. We saw that a subgroup of patients with NASH have relatively low levels of leptin in contrast to the amount of body fat they had. We now would like to see if restoring leptin levels to normal will improve the disease process in these patients. Our study patients will be male patients, aged between 18 and 65 (inclusive), who do not have any other cause for their liver disease. We have put some restrictions in body size such that a spectrum of patients from normal weight to obese range would be included. They will also demonstrate low leptin levels (levels similar to only 25% of normal population). We will use a genetically engineered form of leptin manufactured by Amylin Inc. given via injections under the skin. We plan to continue therapy for a period of one year and evaluate the change in liver disease by a liver biopsy. We will also follow the metabolic parameters and body composition characteristics that we examined in our Phase I study. We expect that patients with low blood leptin levels will show improvement in their liver disease and insulin resistance when their blood leptin levels are restored to normal.

Eligibility Criteria:

- ❖ Must have undergone our Phase I study and have biopsy proven NASH
- ❖ Demonstrated low leptin levels
- ❖ Male patients between the age of 18 and 65
- ❖ We exclude all patients with other known causes of liver disease such as viruses and alcohol
- ❖ Patients with advanced liver disease are also ineligible
- ❖ We exclude patients with diabetes mellitus and those who are pregnant or lactating

- ❖ Patients with complicated diseases such as kidney or heart failure are also ineligible

Compensation: \$30 per visit

Duration of study: 18 months for each subject

If you are interested in participating as a subject in this study, please contact Dr. Oral's study coordinator, Valida Bajrovic, at (734) 615-0539.

Contact Us

We are located on the 3rd floor of the Taubman Center, in the University of Michigan Hospital.

Our address is:

The Department of Internal Medicine
Division of Metabolism, Endocrinology and Diabetes
3920 Taubman Center
1500 E. Medical Center Drive
Ann Arbor, MI 48109-0354

To speak directly to Dr. Elif Oral, M.D., please call: (734) 615-7271

To speak to the study coordinator, Valida Bajrovic, please call: (734) 615-0539