Diabetes Research

Ajanta Naidu, MD, MBA, FACE
Associate Professor, Pediatrics
Director, Ped-Endocrinology
UCI Diabetes and Endocrine Center
UCI, Irvine, CA
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Disclaimers

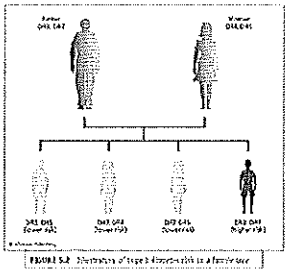
I do not have any personal financial relationships with the companies or products presented

I do not have any family members with financial relationships with the companies or products in discussion

Diabetes Mellitus

- Prevalence: >370 million worldwide
- 50% undiagnosed
- US: ~ 215,000 (1 in 300) young people under the age of 20 have T1 DM
- ~ 3 million Americans have T1DM
- Annual Diagnosis: T1DM 15,600, T2DM 3,600

Genetics



Risks of inheriting diabetes

- If no family history of Diabetes : 11% chance of developing Type 2 Diabetes by age 70 and a 1% chance of Type 1 Diabetes by age 50
- If father has Type 1 Diabetes, 6% chance of Type 1 Diabetes
- If the mother has Type 1 Diabetes and was younger than 25 when the child was born, 4% chance of Type 1 Diabetes
- If the mother has Type 1 Diabetes and was older than 25 when the child was born, 1% chance of Type 1 Diabetes
- The risk of developing Type 1 Diabetes doubles if the parent was diagnosed by age 11
- 10% If a first-degree relative has diabetes
- In identical twins, one twin has only a 33% chance of having type 1 diabetes if the other has it
- If one parent was diagnosed with Type 2 Diabetes before the age of 50: 14% chance of Type 2 Diabetes.

Genetics and Autoimmunity

- T1DM at least 18 genes involved
- Immune attack on beta cells: well before clinical presentation and continues long after diagnosis
- Autoantibodies to glutamate decarboxylase (GAD), IA-2, and to insulin may be positive in the blood in early stages up to 10 years before diagnosis
- Risk of developing diabetes in patient with high-risk genes and all three antibodies, in the next 5 years: >50 %

T1DM

T lymphocyte attack insulin-producing β cells of pancreatic islets of Langerhans

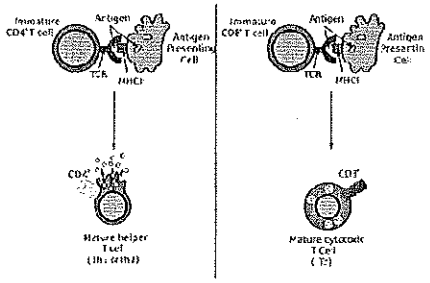
2 stages:

- occult phase - insulitis, with β cell death
- overt phase – diabetes with bulk of β cells destroyed and insulin deficiency

T1DM T cell mediated autoimmune disorder

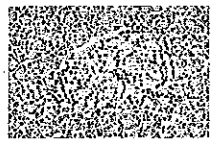
Trauma or infection can release intracellular antigens into the circulation resulting in altered perception of self antigens as foreign by the immune system

Cytotoxicity



Autoimmunity

- IFN-γ is produced predominantly by natural killer (NK) and natural killer T (NKT) cells as part of the innate immune response, and by CD4 Th1 and CD8 cytotoxic T lymphocyte (CTL) effector T cells once antigen-specific immunity develops



Antibodies

1. autoantibodies to islet cells (ICA)
2. autoantibodies to insulin (IAA)
3. glutamic acid decarboxylase autoantibodies (GAD Ab).
4. autoantibodies to tyrosine phosphatases IA-2 & IA-2β

One or more Ab present in 85-90% of individuals with fasting hyperglycemia

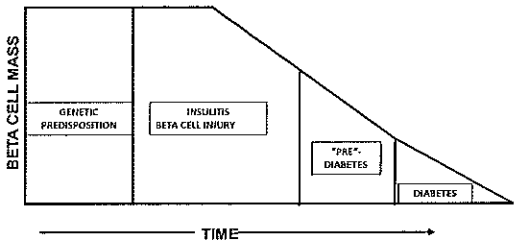
Screening

- ICA, GAD Ab and IAA for screening first-degree relatives of patients with IDDM
- ICA, GAD Ab and IAA appear at random, varying rates depending on the patient
- Antibodies occur before the onset of IDDM, increasing potential for early disease detection
- IAA is among the first to appear during the asymptomatic period of IDDM (lasting years to decades), and is present in majority of young children who become diabetic

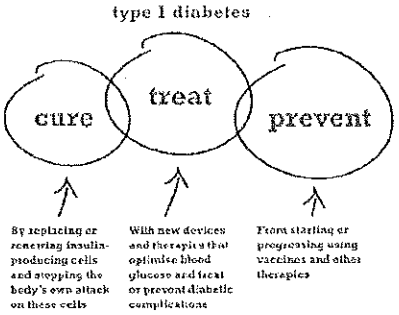
Clinical Utility

- 60-80% of first-degree relatives with both ICA and IAA will develop IDDM within 10 years
- Predictive value for development of TIDM in first-degree relatives increases to 100% when the ICA is strong (>80 JDF U) and persistently positive
- 43% of ICA-positive, first-degree relatives also have elevated GAD Ab

Natural History of Type 1 Diabetes



Intervention Strategies



Areas of Intervention and Solutions

- Identify Areas to Intervene
  - Genetic Predisposition + Environmental Triggers
  - Pre-Diabetes
  - At Diagnosis
  - Years Post-Diagnosis
- Technological Solutions
- Biological Solutions
- Pharmaceutical Treatment
- Nutritional Management
- Complication Prevention/Management

Prevention of Diabetes- Type 1

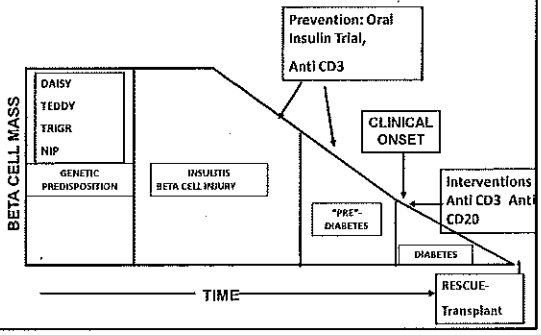
Trialnet and other studies

- Prevention of Insulitis in both genetically at risk and others
- Prevention of Progression from Insulitis to Diabetes

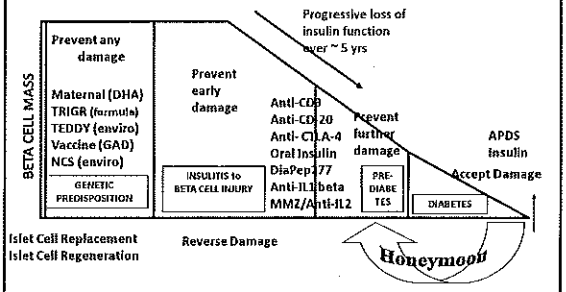
and

Honeymoon Period to Complete Type 1 Diabetes

Natural History of Type 1 Diabetes



Loss of Beta Cell Function and Intervention in Type 1 Diabetes



TEDDY

T he E nvironmental D eterminants of D iabetes in the Y oung – looking for causes of type 1 diabetes mellitus (T1DM)

identification of factors that trigger T1DM or protect from T1DM in genetically susceptible children

- infectious agents
- dietary factors
- environmental agents, including psychosocial factors

In the US: Colorado: Denver , Georgia: Atlanta Augusta, Florida: Gainesville, Washington: Seattle
In Europe: Germany, Sweden, Finland

Nutritional Intervention Prevention NIP

- Learn more about a dietary substance, docosahexaenoic acid (DHA) a natural ingredient in breast milk and in various foods
- To test if giving more DHA will do even more good.

Start early, well before the immune system begins its attack: before 6 months of age, or even before birth

DHA can be found in fish, but in this pilot study, DHA is plant based to avoid concerns about mercury or other toxic contamination

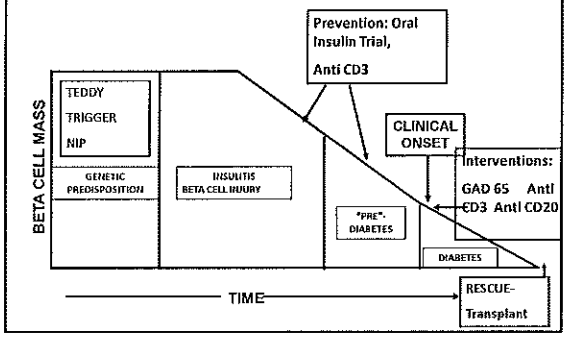
TRIGR

The Trial to Reduce IDDM in the Genetically at Risk (TRIGR) (an international effort- final results of the study available in year 2017)

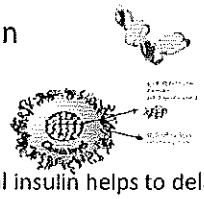
- a primary prevention nutrition trial for insulin-dependent diabetes
- targeted at newborns at genetic risk for type 1 diabetes (mother, father and/or full sibling has type 1 diabetes)

Some evidence that infants at risk for developing type 1 diabetes who were ***fed a specialized formula, hydrolyzed infant formula after breastfeeding were less likely to develop autoantibodies associated with type 1 diabetes, when compared with those who received formula made with cow's milk***

Natural History of Type 1 Diabetes



Oral Insulin



To study if oral insulin helps to delay or prevent type 1 diabetes

Results from a recently completed study (DPT-1) suggest that oral insulin might delay or prevent type 1 diabetes in some people found to be at risk

Anti-CD3 failure

DEFEND-1: a randomized, placebo-controlled Phase III study of 272 patients, age 12 to 45, with new onset T1DM with

otelixizumab, did not meet its primary efficacy endpoint of change in C-peptide levels at 12 months in recently diagnosed patients with type 1 diabetes

Anti-CD3 Antibody

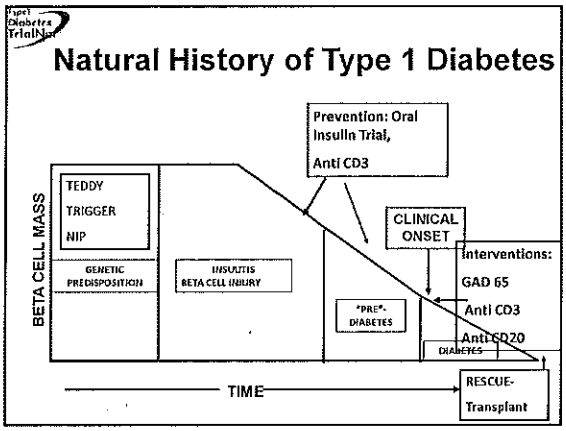
- Teplizumab studied in high-risk relatives with positive antibody and an abnormal glucose tolerance test
- Goal is to delay or prevent onset of T1DM
- 14 days of infusion

Anti-CD3 Antibody Teplizumab

Primary outcome was a comparison of C-peptide responses to a mixed meal after 1 year

- C-peptide levels in the teplizumab-treated group were 17.7% higher
- subgroup analysis showed that treatment benefits were larger in younger individuals and those with HbA1c <6.5% at entry

Diabetologia. 2013 Feb;56(2):391-400. doi: 10.1007/s00125-012-2753-4. Epub 2012 Oct 21.



Diabetes vaccination

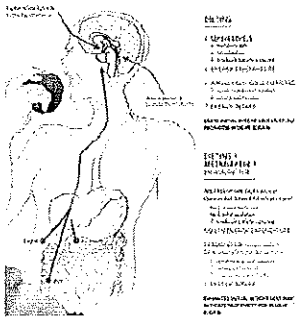
http://diatribe.us/issues/33/new-now-next/10:

- individuals treated with Diamyd did ***not*** show a statistically significant preservation of beta cell function after 15 months of follow-up compared to placebo

Anti CD20 and Anti CD3

Combined treatment with intravenous anti-human CD20 (hCD20) and oral anti-CD3 significantly delayed diabetes development in pre-diabetic hCD20 transgenic NOD (non obese diabetic) mice

Satiety and Leptin



Leptin

Sponsor: University of Texas Southwestern Medical Center

Collaborators: Juvenile Diabetes Research Foundation and Amylin Pharmaceuticals, LLC.

- Metreleptin trials: add leptin therapy to insulin therapy of Type 1 Diabetics
  - aim of lowering the total insulin requirements and suppressing steep fluctuations typically associated with Type 1 Diabetes

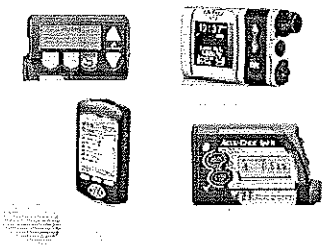
Biotechnology

- Insulin pump
- Glucose sensor – increased accuracy and predictive capabilities
- Augmented insulin pump
  - current sensors may be better at detecting decreasing BGs than increasing BGs. (Ward et al 2011 Diab Med)
- Artificial Pancreas

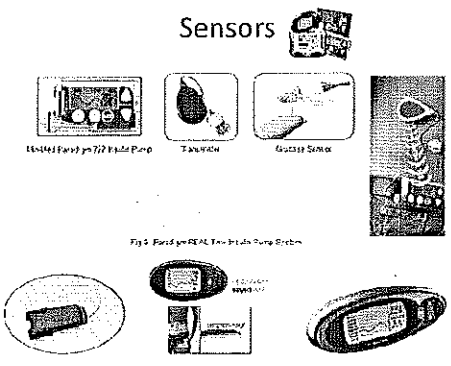
First pump

Newer pump

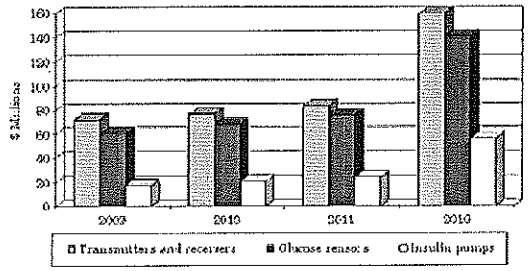
Pumps



Sensors



Pumps and Sensors



Closing the Loop

- Threshold Suspend Device System: avoid hypoglycemia- auto suspend
- Control to Range (CTR): keep BG in target to avoid wide fluctuations
- Control to Target (CTT): tries to achieve set target BGs
- CTR and CTT use:
  - insulin only
  - insulin and glucagon
  - hybrid – using premeal injection + pump to reduce post meal hyperglycemia

Closing the Loop

These devices must

- Detect mechanical sensor/infusion failure
- Detect meal intake
- Be user friendly: to program, lightweight, easy insertion

FDA guidelines and goals

- for reduction in A1C and Hypoglycemia
- population selection

Closed Loop Pump Research

Closed-loop insulin therapy improves glycemic control in children aged <7 years: a randomized controlled trial. Dauber A, Corcia L, Safer J, Agus MS, Einis S, Steil GM. **Source** Division of Endocrinology, Boston Children's Hospital, Boston, MA, USA.

- Diabetes Care. 2013 Feb;36(2):222-7. doi: 10.2337/dc12-1079. Epub 2012 Oct 1
- Results: There was no difference in peak postprandial glucose or number of episodes of hypoglycemia. Conclusions: decreases the severity of overnight hyperglycemia without increasing the incidence of hypoglycemia. The therapy is better able to reestablish target glucose levels in advance of a subsequent meal.

Artificial Pancreas Research

An artificial pancreas device system (APDS)—"closed-loop" system or an "autonomous system for glycemic control."

- automatically monitors blood glucose and provides appropriate insulin doses
- a computer-controlled algorithm connects the CGM and insulin infusion pump for continuous communication between the two devices

Animas First Generation Closed Loop Insulin Delivery System

WEST CHESTER, Pennsylvania, Feb. 28, 2013 /PRNewswire/ --

Data presented at the Advanced Technologies & Treatments for Diabetes (ATTD) Conference in Paris, France.

Animas Corporation announced positive results from the

second phase of human clinical trials:

prediction of rise or fall in blood glucose

and

correspondingly increase, decrease, suspend and resume insulin delivery

Smart Phone Enabled System

Wearable artificial pancreas platform, known as DiAs (Diabetes Assistant), which consists of a smart phone running CTR and connected to standard insulin delivery and CGM devices.

"An unblinded, randomized, cross-over design with each patient participating in two 40-hour outpatient admissions."

Principal goal –

- To validate a smart phone-based control-to-range (CTR) system for ambulatory use and to estimate the effect of CTR vs. sensor-augmented pump therapy
- Justify larger outpatient research

DiaPort by Roche

- Accu-Chek DiaPort to perform continuous intraperitoneal insulin delivery
- Indicated for diabetics that are responding sub-optimally to subcutaneous insulin infusion
- 10 cm tube surgically implanted
- Risks of clotting and infection
- ?? Insulin resistence

Smart Insulins

- Superfast
  - Zincless insulin (Biodel- Viaject/Linjeta)
  - Hyaluronidase (Halozyme)
- Glucose responsive Insulin
- New Basal Insulin (Lilly- LY2605541 and LY2963016, Novo- 40-hour degludec (not cleared by FDA)
- Inhaled Insulin- (Afrezza) Mannkind (bought Exubera factory)

Islet Cell Transplantation

- From donor organs into T1DM patients
- Insulin free for more than a decade after transplant
- Limited to most severe cases of diabetes
- Challenges include 3 Ss
- Supply: not enough insulin producing cells available
- Sustainability: long term acceptance of cells by recipients w/o immuno suppressants (anti rejection drugs)
- Site: optimal site in the body to implant

Source: Fetal Tissue

- fresh human fetal pancreatic tissue – high insulin initially but decreased in time
- purified human islets – already differentiated - high insulin initially and remained high but could not further proliferate
- cultured islet tissue – insulin content increased over 3 months, cells proliferated (replicated) and differentiated (specialize) into functioning tissue

Source: Adult Tissue

Fred Levine and his colleagues at the University of California, San Diego

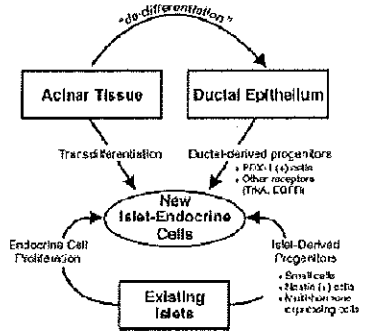
engineered islet cells isolated from human cadavers by adding to the cells' DNA special genes that **stimulate cell proliferation**

- cell lines **further engineered** to express the **beta islet cell gene, PDX-1**, which **stimulates the expression of the insulin gene**
- such cell lines propagate in culture and can be induced to differentiate to cells, which produce insulin

Embryonic Stem cells

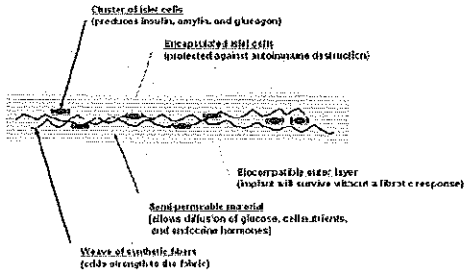
- source of islet progenitor cells lies in the cells that line the pancreatic ducts
- a line of embryonic stem cells could be grown as needed for transplant and engineered to avoid immune rejection
- some evidence that differentiated cells derived from embryonic stem cells might be less likely to cause immune rejection

Ductal Epithelium Cells to generate Islet Cells

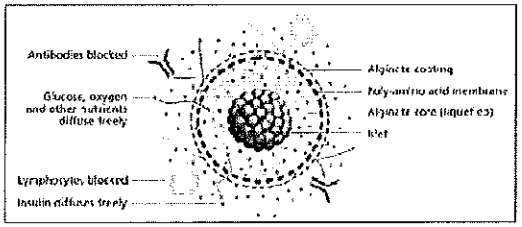


Islet Cell Macoencapsulation

The "Bio-artificial Pancreas" using Islet Sheet technology



Islet Cell Microencapsulation



DRI

BioHub: bioengineered "mini organ" that mimics the islets of the pancreatic gland

Contains real insulin producing cells that release a precise amount of insulin in response to blood sugar

final goal - "cure of diabetes"

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BioHub

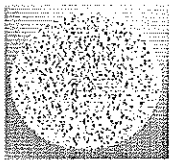
Replicate cellular environment and fine tuning cellular needs within the transplant site:

- Islets are gently seeded into a protective, porous, spongy material with cells nestling within the pores
- Patient's veinous sacs

Environment

- Help promote long term cellular survival and function by

- Additional oxygen (blue)
- Helper cells (yellow)



Porous, sponge-like material the size of a quarter.
Thousands of islet cells (red) nestle within the small pores.
and other agents can be added to a BioHub to keep islet cells healthy, protected and able to function long term.

Prevention T2DM

Prevention Strategies for children and teens at risk:

Support and educate the entire family to make lifestyle changes to delay or lower the risk for onset of type 2 diabetes

Lifestyle changes to maintain healthy weight

- healthy meal choices
- staying active

Guidelines: PEDIATRICS Volume 131, Number 2, February 2013

Surgery

Candidates for surgery:

- BMI of at least 40 kg/m2 and identifiable physical or psychosocial comorbidity of obesity
- As with adults, teens considering surgery should have demonstrated failure of non-operative weight management approaches

Surgery should not represent a first-line intervention

Weight Loss Drugs

- Orlistat
- Metformin
- Acarbose
- Octreotide
- Exanetide (Byetta)
- Topiramate (no studies in childhood obesity)

- Pharmacotherapy should be reserved for those with **significant, severe** comorbidities who have not responded to lifestyle modification.

Research

Studies to learn ways to prevent and manage type 2 diabetes in kids and teens:

- **The SEARCH for Diabetes in Youth Study** : how many kids and teens have type 2 diabetes
- **The TODAY Trial** : best ways to treat type 2 diabetes in kids and teens
- **The HEALTHY Study:** testing a program to lower risk factors for type 2 diabetes in middle school students

GLP-1 for adolescent obesity

Preliminary evidence from a clinical trial suggests that treatment with glucagon-like peptide-1 (GLP-1) receptor agonists was associated with reduced body mass index and body weight in adolescents with severe obesity

Exenatide caused a greater reduction in BMI compared with placebo (-2.7 percent).

JAMA Pediatr. Published online February 4, 2013. doi:10.1001/jamapediatrics.2013.1045.

Medication Interventions in Type 2 DM

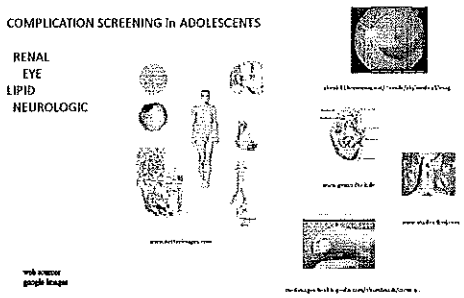
- Colesevelam Pediatric **Type 2 Diabetes** Mellitus Study (WELKid DM) to evaluate clinical safety and efficacy in patients aged 10-17 years

Study Hypothesis: Colesevelam oral suspension for pediatric subjects with T2DM is safe, well tolerated, and shows improved blood sugar control (as evidenced by a significant change from baseline in hemoglobin A1C [HbA1c])

Newer Drugs for T2DM

- DPP-4 Inhibitors (dipeptidyl peptidase) Juvisync (Sitagliptin and simvastatin)
- SGLT2 inhibitors (increase renal loss of glucose)
- Glucokinase agonists (lower set point for insulin release)
- GPR40 agonists- (enhance insulin release)
- 11 beta hydroxysteroid inhibitor (decrease counterregulatory hormones)
- Glucagon receptor antagonist (decrease gluconeogenesis and glycogenolysis)
- Glycogen inhibitors (decrease stored glucose)

Monitoring and Managing COMPLICATIONS



CHOC Research

- TrialNet: affiliated with Stanford: screening and monitoring
- TrialNet Oral Insulin Study
- TID Exchange Project (National Surveillance Registry)
- Novo Nordisk Insulin Degludec vs Detemir in children age 1-5
- TEENS: Glycemic controla nd QofL
- Metformin Therapy for Overweight Adolescent with Type 1 Diabetes

Disclosures

- Research:
  - CHOC Children's receives funding from the NIH for work on TrialNet
  - CHOC Children's receives funding from the Leona Helmsley Trust for work on the T1DExchange
  - CHOC Children's received funding for research done on the Diamyd study

References

- http://www.ncbi.nlm.nih.gov/pubmed/23086558
- http://www.diabetesresearch.org/document.doc?id=530
- PEDIATRICS Volume 131, Number 2, February 2013

Acknowledgements:

- Drs. Daniels, Cortez, Buckingham
- Heather Speer
- Google Images

Short Bio

Dr. Ajanta Naidu

- Ajanta Naidu is a Board Certified Pediatric Endocrinologist and a Fellow of the American College of Endocrinology, in practice for over 28 years. After finishing her pediatric residency at St Lukes-Roosevelt Hospital and Medical Center in New York City, Dr. Naidu completed her fellowship in Pediatric Endocrinology at Nassau County Medical Center in Long Island, New York.

- Dr. Naidu was staff attending at University of California, San Diego for fifteen years and in private practice in Los Angeles for six years before becoming a full time staff attending at UCI Medical Center and holds an academic appointment at University of California, Irvine as Associate Clinical Professor. She is currently Director of Pediatric-Endocrinology at the UCI Diabetes and Endocrine Center.

- Dr. Naidu obtained a MBA degree after completing a 2 year course in HealthCare Executive MBA at the Paul Merage School of Business, University of California, Irvine.

- She was awarded: Dean's Scholar Award, Healthcare Executive MBA at UCI, Irvine, CA August 2011 and Physician of the Year award, Outpatient Center, Miller Children's Hospital, Long Beach Medical Center, Long Beach, CA November 21, 2003

- She is a member of AACE (American Association of Clinical Endocrinologists), Pediatric Endocrine Society, The Endocrine Society and American College of Physician Executives.