From Mentee to Mentor:
Vive La (Hormone) Résistance

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• Clinical Trial Consultant: Daiichi-Sankyo
• Research Contract: Eli Lilly, Inc., Endo Pharmaceuticals, Ipsen, Novo Nordisk, and Versartis
• Advisory Board: Endo Pharmaceuticals, Ipsen, Pfizer, and Sandoz
• Research Grants: Genentech, Inc. and Novo Nordisk
• Royalties: McGraw Hill and UpToDate®

- HRP official journal
- Visiting Fellowship program
- Improved relations with ES and PENS
- Rare Disorders, SCAMPs®, and PIM
- International outreach
- Mentor-Mentee program
How to Be a Good Mentor

• Provide feedback, constructive criticism, and encouragement
• Foster, support, and empower the mentee’s independence
• Have good communication skills
• Be easily accessible and meet regularly
• Inspire, be a role model, and lead by example
• Introduce the mentee to colleagues and help establish networks
• Occasionally be a bit of a tor-mentor!
How to Be a Good Mentee

• Be ready to work at the relationship
• Be open-minded and willing to learn
• Be honest and real
• Be proactive and take initiative
• Be prepared for your meetings with your mentor
• Be a good listener
• Question things that don’t make sense
Reciprocity of Mentor-Mentee Relationship

• Contribute mutual benefits
• Teach each other
• Share excitement
• Appreciate each other
• Give constructive feedback and share success
NIH: Importance of Mentoring

• In addition to providing training, research infrastructure, and salary support for junior faculty and new investigators, CTSA program, consistent with NIH’s K12 Roadmap and Clinical Research Curriculum Award (K30) programs, has identified mentoring as a critical element in assisting new researchers as they become independent investigators

• Mentored NIH K Awards: K01, K08, K07, K12, K23, K25, and K99:
  – 2 – 5 years in length
  – Provide salary support, but limited research funding
  – Associated with loan repayment program
  – Contain both a career development plan and a research plan
  – Includes a team of mentors, co-mentors, advisors, etc.
  – Goal: transition to research “independence”
Mentoring Starts at Home
Hormone Resistance: Historical Perspective

The concept that hormone resistance could cause endocrinological dysfunction was first suggested by Albright in 1942 as the mechanism for parathyroid hormone (PTH) unresponsiveness in pseudohypoparathyroidism.
Mechanisms of Hormone Resistance

- **Intrinsic or primary defects**
  - tend to be rare
  - are genetically mediated within target cell
  - persist in cultured cell models

- **Extrinsic or secondary defects**
  - result from circulating serum factors
  - are reversible following therapeutic perturbations that remove resistance-causing factor from bloodstream
  - do not persist in cultured cells
IN LEARNING
YOU WILL TEACH
AND IN TEACHING
YOU WILL LEARN

Phil Collins
Case History and Physical Examination

- 2.5-yr-old male with history of 2 convulsions, each associated with prolonged fasting and one with documented laboratory BG = 28 mg/dL
- 1-yr h/o darkening of skin
- Chronic redness of eyes
- Difficulty swallowing solid foods
- PE: wt @ 5th %ile; ht @ 25th %ile; hyperpigmentation on lips, tongue, pressure points, and areas of skin trauma; and fungiform papillae on tongue
2 years
Laboratory Data

- Fasting glucose = 10 mg/dL
- Sodium = 127 mmol/L
- Potassium = 4.8 mmol/L
- 8:00 AM cortisol = undetectable (5-24 µg/dL)
- 8:00 AM ACTH = > 2000 pg/mL (20-100)
- 30' and 60' post-Cortrosyn® (1,24-ACTH) cortisol levels remained undetectable
Fig. 2. Responsiveness of the zona glomerulosa to stimulation by the renin-angiotensin system. Aldosterone (*left-hand bars*) and serum renin concentration (*right-hand bars*) responses before and after 1 mg/kg of intravenous furosemide (resulting in an 8 ml/h diuresis) and 1 h of upright posture are shown. The resultant salt-water depletion physiologically activates the renin-angiotensin system and, secondarily, aldosterone release by the zona glomerulosa.

Fig. 1. Responsiveness of the zona glomerulosa to cortrosyn (ACTH). Aldosterone (left-hand bars) responses before and after 0.25 mg of intravenous Cortrosyn are shown. Elimination of postural effects is shown by the lack of concomitant significant serum renin concentration rise (right-hand bars).

Fig. 3. Effect of theophylline on cortisol production. Intravenous theophylline was administered at age 2½ years as a loading dose of 5 mg/kg followed by an infusion of 1.0 mg/kg/h for 2 h. Two hours after the theophylline infusion was initiated, serum cortisol was detectable for the first time at a concentration of 7.5 µg/dl, and was still detectable at a concentration of 3.5 µg/dl 2 h after the infusion was terminated.
Schematic Representation of the Role of MC2R and MRAP in ACTH Signaling

Ramachandrappa S, et al. Front Endocrinol (Lausanne) 2013;Feb 8;4:9
Allgrove Syndrome [AAA(A)S]

- **Clinical:** Rare, familial, and AR with clinical features of FGD +:
  - Adrenal insufficiency
  - **Achalasia** (inability of LES to relax leading to difficulty swallowing)
  - **Alacrima** (absence of tears), neuropathy (sensory impairment, motor
  - Autonomic neuropathy, and MR), and, in some patients hyperkeratosis of palms and soles

- **Mechanism:** AAAS gene encoding ALADIN postulated to be involved either in:
  - Nucleo-cytoplasmic trafficking
  - Peroxisomal activities
Mentoring is a two-way street. You get out what you put in.

Steve Washington, CEO & Co-Founder of Casentric
Serum insulin = 10,975 µU/mL
## GnRH Stimulation Test

<table>
<thead>
<tr>
<th>Test</th>
<th>0'</th>
<th>30'</th>
<th>60'</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH (mIU/mL)</td>
<td>2.5</td>
<td>2.6</td>
<td>2.2</td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>180</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrone (pg/mL)</td>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone (ng/dL)</td>
<td>76</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2 weeks

3 months

Fox LA, et al. AJDC 1992;146:896-898
Leprechaunism

- **Clinical Features**: Autosomal recessive inheritance, frequent consanguinity, intrauterine and postnatal growth retardation, dysmorphic facies, lipoatrophy, muscle wasting, acanthosis nigricans, ovarian hyperandrogenism in females, precocious puberty, hypertrophic cardiomyopathy, and early death
- **Mechanism**: Insulin-receptor gene mutations in all cases
Specificity Spillover

• In states of resistance to hormone action, serum [hormone] usually increases, on occasion by orders of magnitude, via negative feedback.

• High serum [hormone] can transduce certain hormone actions through receptor-effector pathway different from, but homologous to, natural hormone receptor-effector, i.e., via specificity spillover through “promiscuous receptors.”
Structure, Tissue Distribution, and Ligand Binding Affinity of IR-A, IR-B, and IGF1R


<table>
<thead>
<tr>
<th>Predominant expression</th>
<th>Spleen</th>
<th>Liver</th>
<th>Ubiquitous</th>
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<tbody>
<tr>
<td></td>
<td>Brain</td>
<td>Fat</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphocytes</td>
<td>Muscle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placenta</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fetus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin (nM)</td>
<td>0.2 – 0.9</td>
<td>0.5 – 1.6</td>
<td>&gt; 100 – &gt;1000</td>
</tr>
<tr>
<td>IC50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF2 (nM)</td>
<td>2.2 – 2.5</td>
<td>10 – 1.6</td>
<td>0.5 – 4.4</td>
</tr>
<tr>
<td>IGF1 (nM)</td>
<td>9.0 – 41</td>
<td>90 – 390</td>
<td>0.2 – 0.8</td>
</tr>
</tbody>
</table>
Selective Insulin Action in Insulin-Resistant States

- Insulin Receptor Type 1
- IGF Receptor
- ↑INSULIN
- Acanthosis Nigricans
- Polycystic Ovary
- Myocardial Hypertrophy
Leprechaunism

*αIR-3 = antibody against type 1 IGF receptor

Clinical Spectrum of Insulin Receptoropathies

It's so essential to surround yourself with individuals who are already where you want to be.
GH Receptor (GHR) Defects (Laron syndrome)

- Autosomal recessive (typically) cause of severe short stature most commonly found in inbred populations of Middle East
- Phenotypically resembles GHD, except that serum [GH] are elevated and, in most cases, circulating [GHBP] are low or absent
- Most patients have mutations affecting EC domain of GHR, including exonic deletions; frameshift, nonsense, and missense mutations; and splicing defects
- Do not grow in response to endogenous or exogenous GH, but respond, at least in part, to IGF-I therapy
Laron Dwarfs: GH Responsiveness

Geffner ME, et al. JCEM 1987;64:1042-1046
Laron Dwarfs: IGF-I Responsiveness

Geffner ME, et al. JCEM 1987;64:1042-1046
Mentoring

Successful People never Reach their goals Alone.
Pygmies

- Short-statured peoples typically thought of as residing in equatorial Africa, but also found in other parts of the world, e.g., New Guinea

- Their short stature is thought to be adaptive in terms of:
  - Ease of locomotion through dense forest understory
  - Minimization of food requirements during cyclical periods of undernutrition
  - Selection for survival in hot, humid forest environment where greater surface area : body mass is necessary for sufficient thermoregulation

- Short stature originally thought to result from GH resistance and absent adolescent growth spurt
Geffner ME, et al. JCEM 1995;80:3732-3738

GH RESPONSIVENESS

Colony (% of control)

Pygmies (n=7)
Lese (n=3)
American controls (n=4)

GH (μg/L)

PBS
IGF-1 RESPONSIVENESS

Colones (% of control)

PBS

IGF-I (μg/L)

- Pygmy (n=7)
- Lese (n=3)
- American controls (n=5)

Geffner ME, et al. JCEM 1995;80:3732-3738
Geffner ME, et al. JCEM 1995; 80:3732-3738
Geffner ME, et al. JCEM 1990;71;464-469
## Variations in cDNA Sequence of Type 1 IGF Receptor in Efe Pygmies

<table>
<thead>
<tr>
<th>Previous report</th>
<th>Sequence variation</th>
<th>Location</th>
<th>J-RN</th>
<th>Pygmy</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

2827ACAGGA → AGA  
ThrGly (ThrGly)  
EC domain of β-chain  
+ + + + + + +

2869GTC → ATC  
Val (Val)  
Transmembrane  
- - + - - + +

GGC3555 → GGG  
Gly (Gly)  
Tyrosine kinase domain  
ND + ND ND ND ND ND

TAC4083 → TAT  
Tyr (Tyr)  
C-terminus  
- + - + - - -

Hattori Y, et al. JCEM 1996;81:2257-2263
African Efe Pygmies: Summary of Mechanism of Short Stature

- Although early studies suggested that GH resistance was responsible for their short stature, more recent work has demonstrated genetically-regulated combined GH and IGF-I resistance in African (Efe) Pygmies.
- Underlying variation appears to be primary IGF-I resistance with secondary GH resistance.
- Neighboring Lese Africans, whose gene pool is intermingled with that of Efe, show intermediate responses to both GH and IGF-I.
- To date, no mutation has been found in type 1 IGF receptor gene of Efe Pygmies.
- In Bantu Pygmies, genetic association studies have implicated loci on chromosome 3, including DOCK3, known to be associated with height variation in Europeans and CISH, a negative regulator of cytokine signaling known to inhibit GH-stimulated STAT5 signaling.
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Behind every…President is…
Famous mentees and their mentors

- **OPRAH WINFREY** mentored by Mrs. Duncan (4th grade teacher)
- **GEN. COLIN POWELL** mentored by his father Luther Powell
- **DR. MARTIN LUTHER KING** mentored by Dr. Benjamin E. Mays
- **LUKE SKYWALKER** mentored by Obi-Wan Ben Kenobi (*Star Wars*)