# Grant Writing

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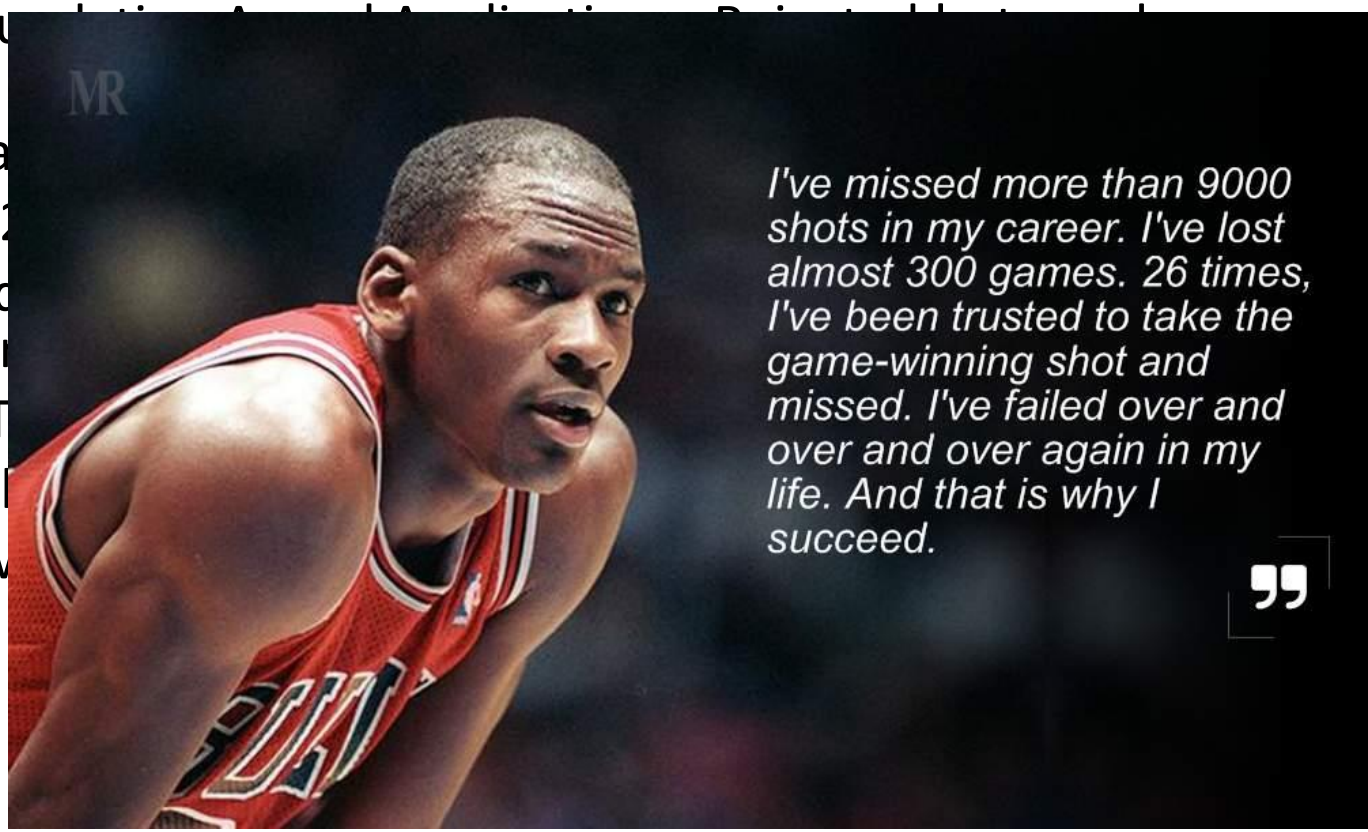
# “Many receive advice, only the wise profit from it” – Harper Lee

- There are many ‘grant writing’ courses many of which are based on ‘successful grants’.
- Such successful grants share certain common terms, design features and styles
  - This presentation won’t review those formulaic versions of grant writing specifically but will focus on how to design studies and then how to communicate essential elements clearly

# A little about me

- First pilot grant written in 1998; shopped around to 5 different mechanisms before it was funded
- Second pilot grant in 1999; funded on second try
- AHA Bugher Fou
  reviews
- K-23 award – Fa
- 10 failed R01/R2
- Since then, func
  the past 15 year
- NINDS Clinical T
- Ad hoc, then ful
- Editorial Review



# What are the worst ways to write a grant?

- “I really need a grant to be successful!”
- “My chairman says that they won’t protect my time forever. I HAVE TO GET FUNDED!”
- “I won’t be an independent investigator until I have an R01!”
- “If I don’t have two R01s, I won’t make tenure!”
- “There’s $500,000 per year for five years. That’s $2.5 million dollars…how should I spend money on science?”
- “That jerk is higher on the NIH funding ranking than me? I’ve got to beat them!”
- “No one will ever fund me to do something really big, that’s out of my reach. I should stay within these safe boundaries…”

# Rule number 1

- ALWAYS think about the best science
  - As opposed to:
    - No one will fund me for the best science but this is something “safe”
    - Others were successful doing __ so I should do that
    - This RFA has $50,000 per year for 5 years; how should I spend that money?

# Example

- RNA-sequencing of leukocytes gives the gene expression pattern of those cells
- Let's do an RNA-seq in ICH!

- Well….that doesn't START with the best science you can think of. Why do this?
- Well, we know that ICH causes a marked serum inflammatory response but so would any major medical event. Is there reason to believe that this is anything but demargination?
- We could look at the WBC differential and see if there is any part of it that is independent of the severity of the ICH itself

- Therefore, the 'best science' would be to first see if the leukocytes make a difference in outcomes independent of the severity of ICH itself

# Example

- IVH is bad, we have a cool device to remove IVH, let's remove it!

- Well, not ALL IVH is bad. Some IVH probably doesn't do anything. We need to have some criteria for who we'll remove the IVH in. We don't want to do more harm than good.
- And, is the 'damage' already done and removing the IVH wouldn't reverse it?

- Basically, whatever idea you have could probably be better than when you first thought of it.
  - Be ready to jettison an idea with a fatal flaw
  - Be ready to modify and improve and perfect from your original design
  - Be ready to find collaborators with the expertise you need to accomplish the best science you can

# The Scientific Method

- Observation
- Question
- Hypothesis
- Predict based on the Hypothesis
- Test
- Iterate to new Hypotheses

# The Scientific Method

- Observation
  - Observational studies include case series, case-control, surveys, cohort studies
  - May also be a literature review
  - Observational studies or data build the foundation for most research.

# The Scientific Method

- Questions:
  - Any number of questions may be asked but it's important in research to understand that these questions should be:
    - Novel or needs additional evidence
    - Consider having a conceptual model that explains the observation
    - Starts with observations, best if you can cite it
  - For example: If women have more aneurysms than men, how are women different from men? Is it estrogen? Is it uterine? Is it vascular? Is it height? Is it weight? Is it pregnancy related or menopausal related or progesterone related?

# The Scientific Method

- Hypotheses:
  - A hypothesis is a testable explanation of the observed phenomenon
  - "If ___ is true, then ___ should happen" is a VERY strong testable explanation or hypothesis
- Some common errors:
  - Statements – A statement may have an implied question it but usually best to clarify into a question. "Women are more likely to have aneurysm than men because they have a higher estrogen burden" is a statement with an implied hypothesis.
  - Try: If higher estrogen burden is a higher risk of aneurysm, then women with low estrogen burden will have lower occurrence of aneurysm than those with higher estrogen burden"
  - Too many hypotheses in the hypothesis: "We will test the hypothesis that women are more likely to have aneurysms because of higher estrogen burden over time in pre and post-menopausal states compared to men and burden of hormones including progesterone and testosterone."
  - Too few considerations in the hypothesis: In the above example, what about progesterone? What about surgery? What about age of menarche or surgical menopause or use of hormone replacement therapy?" All of these can be added into the hypothesis but still be part of the overarching hypothesis unlike the prior example where each item was a different hypothesis.

# What's a specific aim?

- What will be the scientific achievement or advance that the study will achieve? What are you specifically trying to accomplish?
- Typically a 'task' is not a specific aim unless the task is so large it is of itself a major accomplishment
- Determine, establish, identify are common scientific aims
- How will your work advance the field?
- "So what?" if the study is positive or negative

# Some examples

- Specific Aim 1: We will recruit 200 cases of aneurysm in women and men.
  - This isn't really a scientific aim, it's a task!
- Specific Aim 1: We will test the hypothesis that higher estrogen burden is associated with higher risk of aneurysm formation.
  - This is a hypothesis, not an aim!
- Specific Aim 1: Through these experiments, we will establish if higher estrogen is associated with aneurysm formation independent of all other risk factors.

# On dependent aims

- Aim 1: We will determine if inflammation is present based on RNA sequencing chronically (>1 year) after spontaneous intracerebral hemorrhage
- Aim 2: We will validate findings from Aim 1 utilizing protein measurements of significant and independent findings

- The above is an example of dependent aims (fatally flawed!)
- Truly, this is ONE aim which should be written:
- We will determine and validate whether inflammation is present by RNA sequencing and protein measurements occurring >1 year after spontaneous intracerebral hemrorhage.

- So then what's Aim 2? That's the trick! Need to think of something else to do.

# How to design a grant

- Prior to but also during the writing of a grant, one is ‘designing the grant’
- You are seeking to put forth the ‘best possible science’ that you can think of.
- What is the ‘best science’?
  - It’s typically judged on it’s impact into the field which can be further scaled into:
    - Significance: Who cares? Does it impact a lot of people? Does it make a big leap forward to a small group of people?
    - Innovation: Haven’t we done this already? Is this a minor iteration of prior work? Is there a technical innovation?
    - People: Are *you* and your team the right people to do this, even if it’s a great idea?
    - Methods: Is the method you are using well powered, internally and externally valid, robust and reproducible?

# What isn't the 'best science'?

- Hm, this RFA is for $50,000 per year for 5 years…how shall I spend this money?
- I've proven this thing and I want to prove it again
- They'll never fund me to do __ so instead I'll do this thing that they will fund me to do
- Please fund me!

# Solve this problem

- Solve this problem: Women are less likely to have all subtypes of stroke EXCEPT intracranial aneurysm related subarachnoid hemorrhage (SAH) where they have a higher rate of SAH than men.
- Some ‘x’ factor is related to why women are more likely to have aneurysmal SAH than men.
- Solve for X

- Women smoke less and have less hypertension than men yet hypertension and smoking are the greatest risk factors for aneurysmal SAH
- Solve for X

- Women are also shorter than men, have more estrogen, less androgen/testosterone, different body habitus, have two X chromosomes,
- Solve for X

# Solve this problem

- Hopefully you generated some interesting hypotheses as to why there is a gender difference to SAH compared to others.
- Now solve this problem:
- What's my next grant idea?....
- Solve for X

# Vapor Locked?…

- Given a task with a defined set of instructions and education, most scientists will be successful without much difficulty
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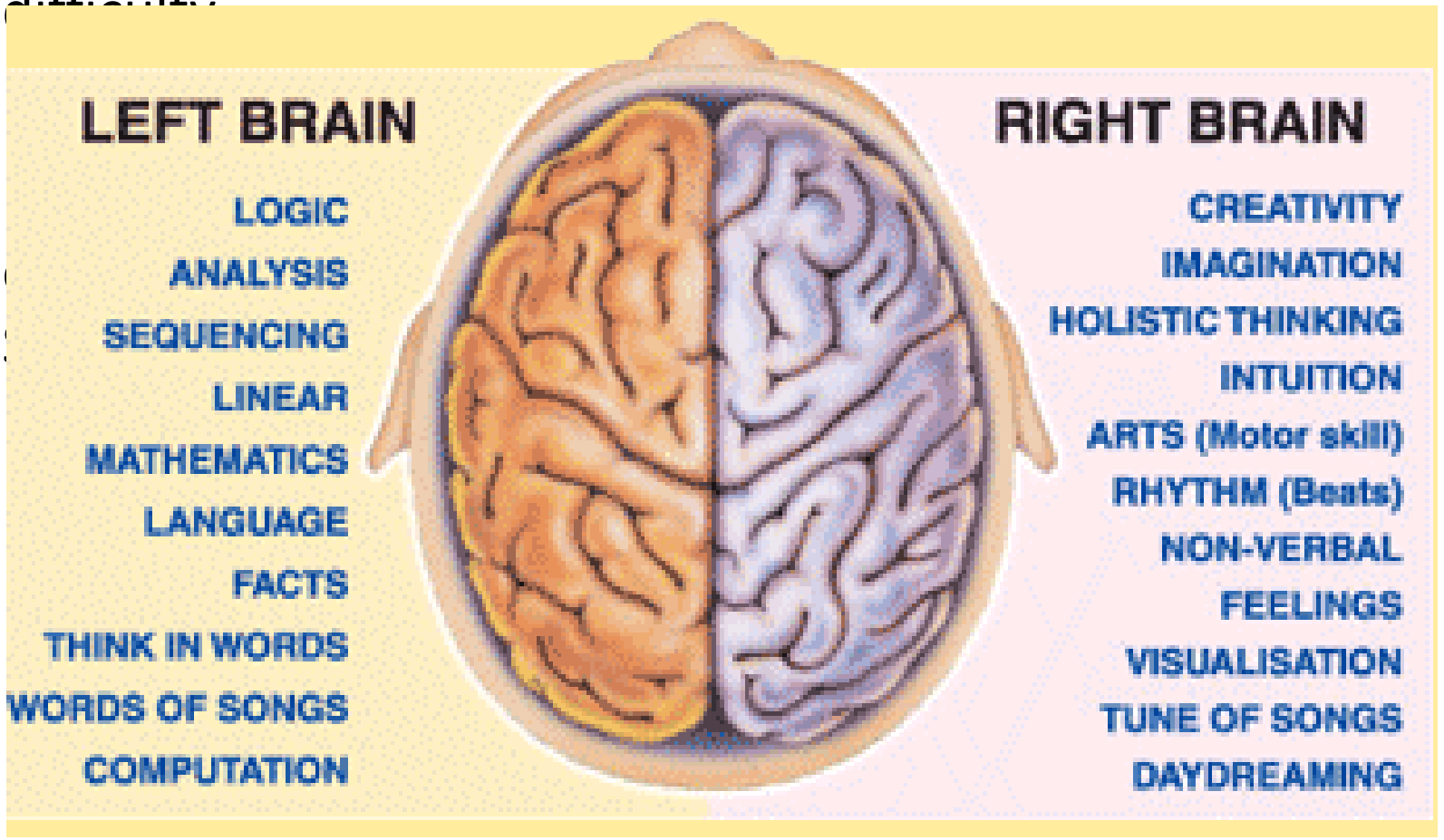

# Big Picture and Detail Oriented

- I have often said that there are three types of successful people in academics
  - Big picture – The person who can see the forest for the trees, make connections between disparate ideas and concepts and facts, grand vision
  - Detail oriented – Methodical detail oriented individual who can master hundreds of moving parts, remember minute detail, rules, facts, figures, handle enormous complexity and detail
  - And the most successful is the person who can do both
- If one considers right brain to be the big picture brain and the left brain to be the detail oriented, then first know which you are. Are you detail oriented, big picture, or both?
  - Practice DEFINITELY alters your brain and pathways. You can 'think' a different way by practicing that way of thinking
  - Most rote, scientific learning is very left brain oriented. Memorization and implementation without mistakes of specific logical, rational pathways and concepts. Detail oriented
  - But some actually teach conceptual model building, intuitive thinking, getting the 'sense' of something or the 'feel' of something.

# Three major types of new grants

- Next logical step
- Same technique, different phenotype
- Inspiration!

# Next Logical Step

- This follows a particular line of research starting with an over-arching hypothesis.
  - Remember, hypotheses are strongest when they begin with an observation that is strong/reliable
  - This doesn't have to be your own line of research although that much stronger if it is.
  - It demonstrates the importance of knowing what it is that you have done and how it fits into the literature.

# Determining the next logical step?

- Try to always remember your over arching hypothesis and continue to test until you can confidently
- Obesity is mediated
  - If true, hypothesis degree relatives sh should have a high environmental exp
  - If true, hypothesize risk of obesity than and era/age
- Studies demonstrate there is a gene or a obesity or makes an
  - If true, a genome w obesity or protecti
  - If true, a family-bas protection from ob
- GWAS studies identi association with obe


Abstract

Until just a few years ago, the genetic determinants of obesity and metabolic syndrome were largely unknown, with the exception of a few forms of monogenic extreme obesity. Since genome-wide association studies (GWAS) became available, large advances have been made. The first single nucleotide polymorphism robustly associated with increased body mass index (BMI) was in 2007 mapped to a gene with for the time unknown function. This gene, now known as fat mass and obesity associated (*FTO*) has been repeatedly replicated in several ethnicities and is affecting obesity by regulating appetite. Since the first report from a GWAS of obesity, an increasing number of markers have been shown to be associated with BMI, other measures of obesity or fat distribution and metabolic syndrome. This systematic review of obesity GWAS will summarize genome-wide significant findings for obesity and metabolic syndrome and briefly give a few suggestions of what is to be expected in the next few years.


Highlights

• GWAS have greatly increased the knowledge about obesity genetics. • Common forms of obesity are polygenic with small effects sizes of each variant. • The largest genetic effects size on obesity are reported for *FTO* variants. • We expect large advances over the coming years regarding knowledge on gene function.

# What's the next logical step?

- Evaluate what *FTO* does
  - Animal knockout models?
  - Tissue reporter assay models?
  - RNA inhibitors?
- Find more genes?
  - Larger sample size
  - Rare variant analysis
  - Extreme discordant phenotype

# Some

- The ‘next logical step’ is
  it. Some bigger, faster, a
- If you happen to be the
  biggest hound or at leas
- The next logical step can sometimes lack ‘innovation’, be boring or uninspiring.
- Try to make substantial steps, not incremental baby steps.
  - If a choice between a minor increment of the same thing
  - Compared to a substantial leap forward, reviewers will choose the leap forward.

# Some caveats

- The next logical step with a substantial leap forward may be utilizing a skill set that you don’t already have
- Need to learn it, collaborate with those that have it, build teams and yet contribute substantively to the effort.

# Same technique, different phenotype

- An innovative technique has worked successfully in phenotype A
- In particular if there is an advantage to the innovative technique and the technique is applicable to a wide variety of conditions
- Unlike the ‘next logical step’ where the investigator may have to learn a new technique, here an investigator must learn a new phenotype!

# Same technique, different phenotype

- Investigators working on blood pressure refractory to medications invent an implant that can detect high blood pressure and then stimulate the carotid sinus to lower blood pressure
- Small randomized trials succeed and the device is getting approval for use in refractory hypertension.
- What other phenotypes could this be tried in?

## The electronic implant that could control high blood pressure without drugs

- Monitors the signals sent through a nerve in the neck to regulate blood pressure
- If it detects a high reading, it can overwrite the signal, lowering the pressure without drugs

By MARK PRIGG

**PUBLISHED:** 18:12 EST, 13 May 2014 | **UPDATED:** 03:44 EST, 14 May 2014

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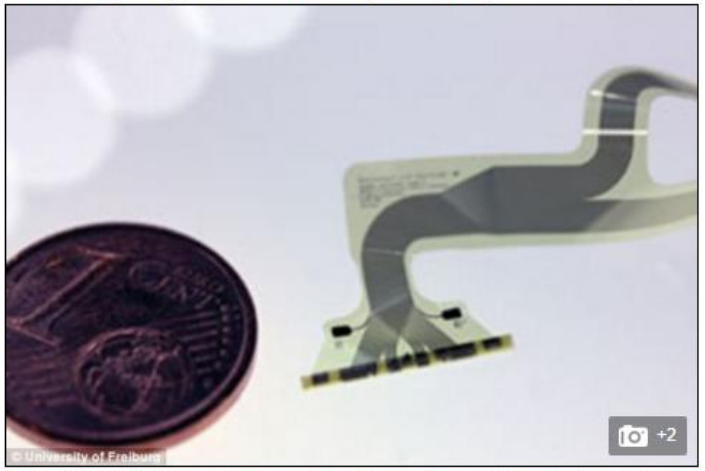
Researchers have unveiled a tiny implantable patch that can automatically monitor and control the wearer's blood pressure.

The German invention monitors the signals sent through a nerve in the neck to regulate blood pressure.

If it detects a high reading, it can overwrite the message, lowering the pressure without drugs.




The German invention monitors the signals sent through a nerve in the neck to regulate blood pressure. If it detects a high reading, it can overwrite the message, lowering the pressure without drugs.

# Same technique, different phenotype

## Google Flu Trends

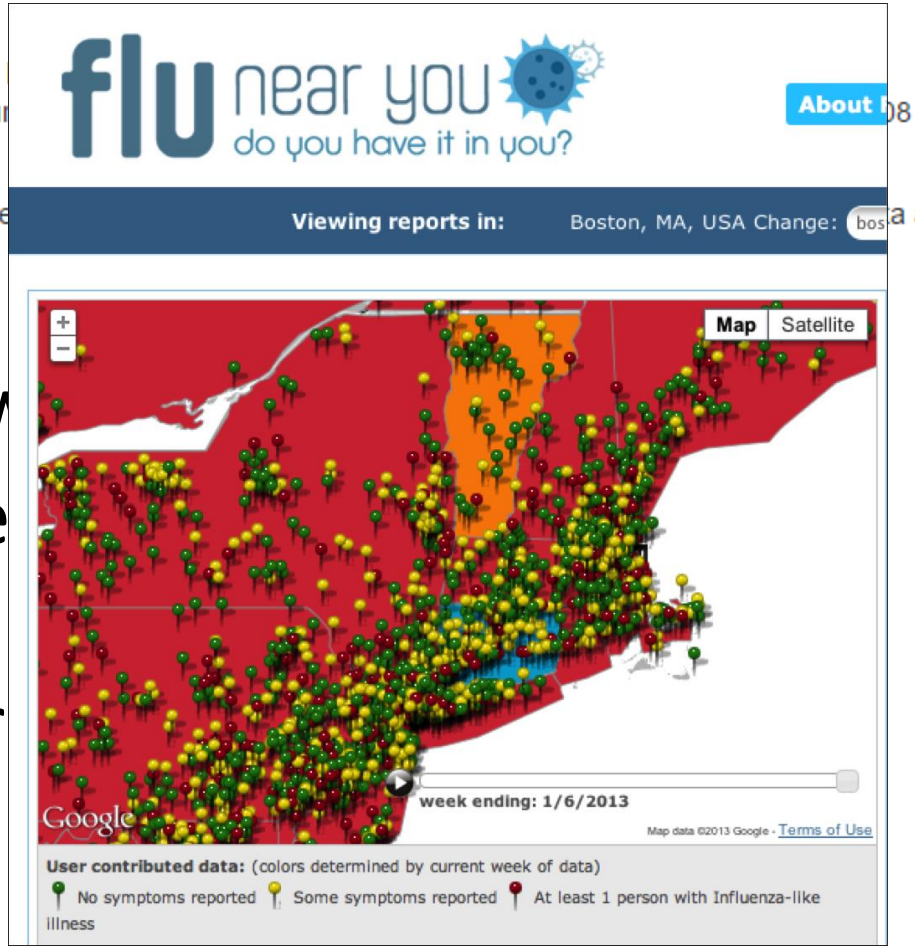
From Wikipedia, the free encyclopedia

**Google Flu Trends** was a web service operated by Google. It
aggregating Google search queries, it attempted to make accu
Google.org to help predict outbreaks of flu.[1]

Google Flu Trends is now no longer publishing current estimate
offered for declared research purposes.[2]

epidemic but Google
same epidemic two w

- The predictions were
  97% accurate!
- Subsequently, it over



# Some caveats

- The technique must be relevant and appropriate to the disease in question
  - Gene expression studies have often failed to progress in acute diseases where the disease itself is likely to affect gene expression
  - OR that the only available tissue was leukocytes
- Need to learn/publish in the new phenotype or partner with those that are experts in that field; build collaborations!

# Paradigm Shift/Inspiration

- Hero, king of Sicily, commissioned a new crown to be made all of gold.
- But when he received the crown, he became very suspicious that the crown was not made all of gold but in fact had mixed in some very cheap silver(!)
- The King commissioned Archimedes to find out if it were pure gold WITHOUT ruining the crown but he wanted proof that it was made purely of gold
- Archimedes struggled with the problem for many weeks but then went to take a hot bath
- In it, he had a moment of inspiration when he noticed, as of course, millions of others had, that when he got in the tub, his body displaced a certain volume of water.

- He then developed an experiment.
- First he acquired pure gold and using a scale created a quantity of gold that was the exact weight of the crown
- He filled a tank with water and put the pure gold in. When he removed the gold, he could measure the amount of water that was displaced.
- He then put in the crown. If the crown displaced exactly the same amount of water, then no water would spill over the edges of the tank and it should reach just to the top
- But, he knew that gold was denser than silver and therefore if silver made up the weight of the crown, it would displace MORE water
- Indeed, the crown did displace more water proving that crown was not made of pure gold!

# Paradigm

- Archimedes took
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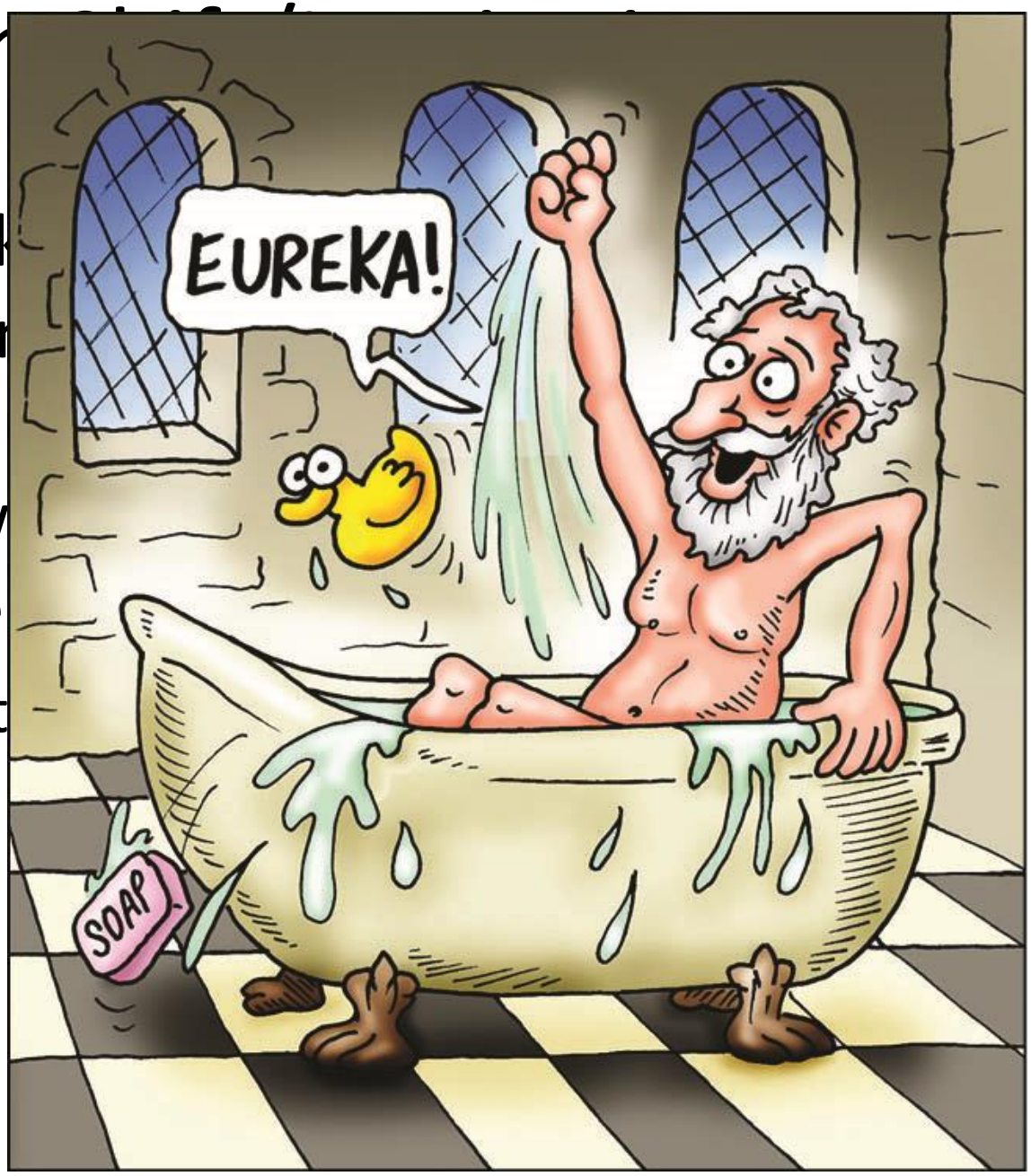
  rising when you
  that had been w
  matter had diffe
  - And combined t
  - EUREKA!

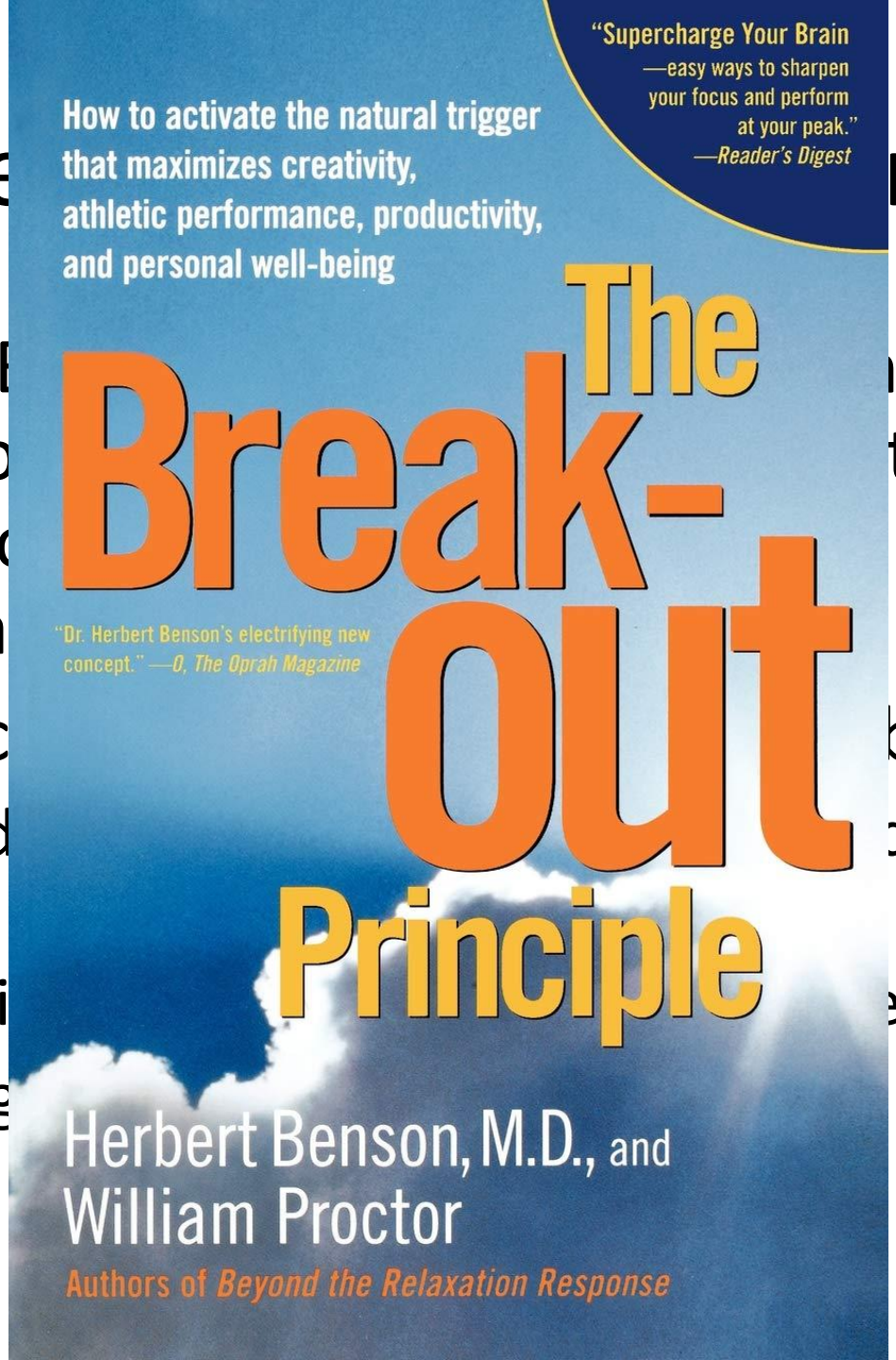


# Paradigm Shift/Inspiration

- There will DEFINITELY be moments when you will see something, a pattern or a combination of two seemingly disparate facts that you can combine together into a new idea/concept
- PAY ATTENTION! Write them down, investigate and search on these. Sometimes, they are the best of all!

# Is there ration?

- Herbert E hor of the Relaxatio trated that meditati pressure; The Brea
- Used Arc breakouts
  - Studied d of time on a topic
  - Then di ent
  - Leading



# Caveats of Inspiration

- Not reliable… ☹
- Sometimes not valid… ☹ ☹ ☹
- Often not believed!
- Or completely unfeasible

> All truth passes through three stages. First, it is ridiculed. Second, it is violently opposed. Third, it is accepted as being self-evident.
>
> Arthur Schopenhauer

# Assessing Ideas

- Significance/Impact
  - Look up the number of people affected by the condition
  - Look up the economic burden
  - The rate of mortality
  - Rate of disability
  - Will the science make substantial advancement towards reducing this?

# Assessing ideas

- Feasibility
  - Effect size estimate to find differences
  - Ability to sample (human or animal)
  - Technologic factors
  - Cost
- Innovation
  - Always see if it's been done before!
  - Innovative in topic, technology or technique
  - Combining two areas into one idea
  - Novel concept or idea being tested

# Assessing Ideas

- Can you do it?
  - Publication record
  - Area of interest
  - Mentorship
  - Support
  - Environment

# Some Tips and Tricks

- Innovation: Technical innovation usually ticks this box off. If you don't have one it's still possible but must be assessed that the techniques applied are truly innovative
- Sex as a biologic variable: Really consider how sex may affect the outcomes or analysis. Don't just include as a covariate.
- Age across the spectrum/race/ethnicity: These unalterable traits are definitely a factor. Do you have enough power? Are you considering the effects on different age groups?
- Internal Validity: Are you doing quality control checks; inter-rater reliability, are your measures supported by the literature?
- External Validity: Is your population representative of the target population? Multi-center, academic and community, reflects the target population
- Robust and Unbiased: Is your sample size sufficient and externally valid

# Study Design

- Why did you design your study the way you did? This is a place to respond to reviewers before you are reviewed!

**Study Design:** Several features of study design rationale deserve discussion.

Educational Attainment as Primary Variable: Key socioeconomic variables and area deprivation indices are available to evaluate and many different combinations of these may be considered. While most of the analyses and writing of the proposal utilizes educational attainment as both a widely prevalent and impactful risk factor for ICH (see preliminary data below), the ready availability of multiple other measures such as pollution, poverty, personal income, household income, insurance status and area and neighborhood deprivation variables will also be explored. Insurance status deserves particular mention in that the advent of the Affordable Care Act over the course of the recruitment period (2008-2016) for the ERICH and GERFHS studies may have variably impacted prevalence by year and is a risk factor which may fluctuate with situation over time. For simplicity in the writing, we utilize educational attainment as a primary example but **fully intend to explore a comprehensive dataset of individual and neighborhood variables** for both independent, additive and interacting impact.

Race as a social construct with critical biologic consequences: As investigators, we agree that race/ethnicity is largely a social construct with critical biologic consequences. In this proposal, principal component analyses may be utilized to define clustered populations with similar genetic background, but we will also use self-reported race/ethnicity which encompasses important social constructs of race. Indeed, much of the social determinants of health that vary by race may have important epigenetic consequences, motivating the current proposal. If we can identify the root manifestations that lead to the higher incidence and earlier age of onset for ICH, we may be able to treat the conditions in all ethnicities.

Sex and age as biologic variables: Our investigators are keenly interested in and have led research regarding earlier presentation by race/ethnicity as well as the impact of sex on risk of ICH and outcomes. Data includes menopausal status, last menstrual period, parity and use of hormonal therapy (male and female). Due to space considerations, preliminary data is not presented on these subtopics specifically but will be explored.

Biologic versus chronologic age: Methylation and other genomic features such as telomere have been purported to represent biologic age and differences in biologic versus chronologic age have been identified. However, our preliminary data from the original submission did not identify substantial impact of either methylation or telomere-based age. Nevertheless, biologic age will be evaluated in secondary analyses but was removed as a primary aim given the lack of preliminary data support.

Multiple Covariates: Our prospective recruitment of cases and controls uses a standardized interview which includes medication and medication compliance, exercise frequency, illicit drug use, alcohol, smoking, and stress. In addition, current household income, household size, as well neighborhood indices such as particulate matter (pollution), traffic, crime, greenspace, and population density are potential covariates within analyses.

Rigor/Robust and Unbiased Results: The current proposal includes over 4,000 disproportionately affected AA and HA cases and controls. Genotyping, CNV calls and methylation will be performed blinded for case/control status and with cases and controls within the same batches. Extensive quality control measures, particularly for false CNV calls, outlier identification and removal and analyses have been addressed in the study design.

# On challenges and barriers

- The first thing we all do when faced with a barrier is to find out how the experts/more experienced people solved the problem or a similar problem
- If it seems reasonable, that's what we do as well
- However, I ask you to consider how YOU would solve the problem if you did NOT have a mentor or expert to give you the answer (be the 10% ant)
  - The difference in my career has been coming up with innovative and creative solutions to problems and barriers; often times bypassing them, flipping them to strengths or advantages, or far exceeding the conventional wisdom solution

# On Reviewers

- Learn why you fail
  - If only the reviewer had read my grant
  - If only I had a reviewer who understood what I was doing
  - What a jerk!

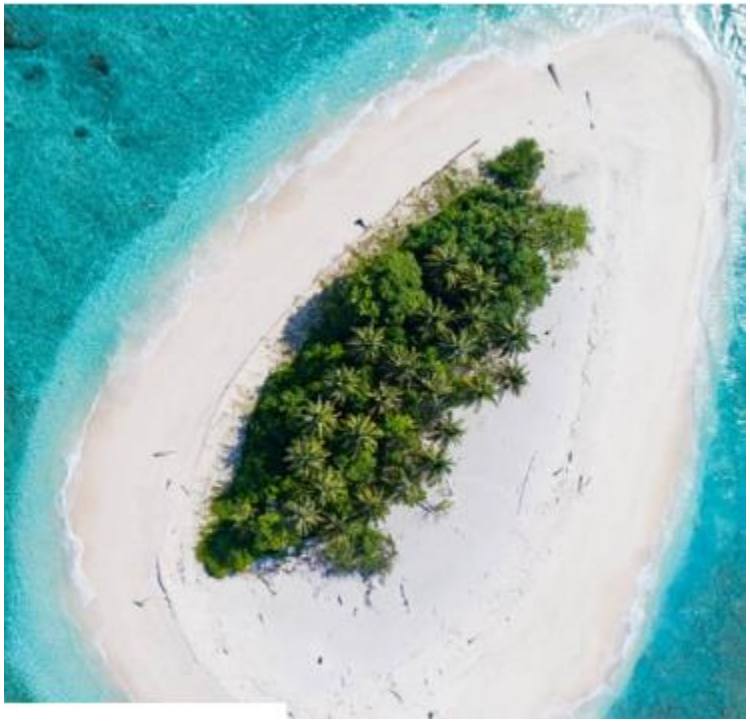
- Actually, the reviewer did read your grant but maybe we didn't write it clearly enough or in a flow that put items where the reviewer expected it or highlighted it.
- The reviewer will never have your particular expertise and you must be ready to write to the intelligent non-expert.
- Have to remove the emotion, hostility, pejorative comments, words and phrases and somehow find the 'point' that the reviewer is (unnecessarily) harshly trying to make and address that point (dispassionately).

# On Reviewers

- Reviewers also come in ‘big picture’ and ‘detailed oriented’ types.
- On writing grants, you have to make sure that the big picture person doesn’t get lost in a blizzard of detail while somehow making sure you are covering the detail oriented reviewers ‘yes, but what about…’ concerns.
- Useful to have both types of people pre-reviewing your grants. Are you losing the big picture mentor or the detail oriented mentor?
- Try to weave detail in very clear and easy to understand language that tells a story and has a flow. This should give the detail without losing the big picture.
- It’s almost always better to give both strengths and limitations of the work you are citing or your preliminary data and even your own study design.

# Imagine you're on a desert island

- You want to get off the island and you have some tools and trees around. So you decide you're going to build a boat!
- You figure 'how hard can it be?'



- But when you go to cut down a tree, you discover it's a LOT harder to cut trees down than you thought it'd be. But after a bit of adjustment, you get a few trees down.
- Now you have to cut some boards but you have absolutely no idea how to do that!
- So you experiment a bit, fail, make some headway and eventually you have the world's ugliest looking boat!
- When you take it down to the shore, the boat actually wobbles as you take it down.
- You are NOT going to trust your life in this boat; so you test it!

- You submit your boat to the Ocean of Criticism…and a huge wave comes up and smashes your boat into smithereens!
- The remnants are pulled away in the tide and you are left standing on the beach with…nothing!
- Your hands are blistered, your back hurts, all of that work for weeks and weeks is now gone!
- You are very…upset!

- But eventually, you get to the same point that all grant writers get to. Which is to realize that
  - Crying is not going to get you off that beach!
  - Feeling sorry for yourself is not going to get you off that beach
  - That the Ocean of Criticism does not care how hard you worked, how long you worked, how nice a person you are or how much you ‘hoped it work’
  - The Ocean of Criticism just wants a leak proof boat
- So you get some rest, wake up the next day, buck up and decide you’re going to build a BETTER BOAT

- And you discover right away that you're much better at cutting down trees than you were the first time around
  - You're selecting the right trees
  - Using the most efficient technique you learned from the last time
  - You're making boards much better, experimenting with things that will make it leak proof
- Eventually, through trial and error and many exposures to the Ocean of Criticism, you finally create a boat that is leakproof and sail away!

- If our goal is to get a grant, we can succeed or we can fail.
- But if our goal is to do the best science, then we are constantly succeeding in learning how to do our science better.

# Final Thought

# Ask me anything!

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