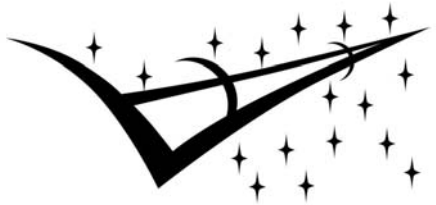
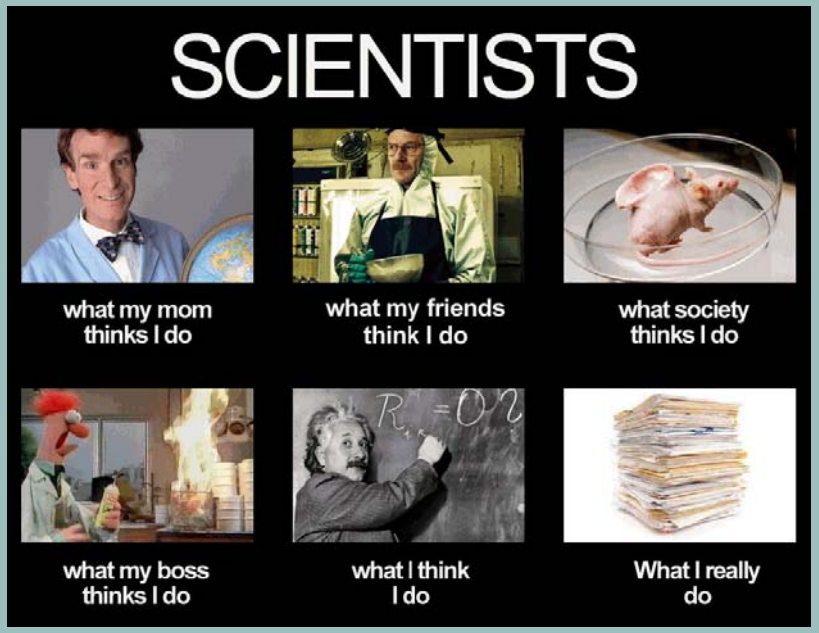
JSC Exit Presentation

Rebecca McFadden
Florida Institute of Technology
Dr. Virginia Wotring
Pharmacology

SPACE LIFE SCIENCES
SUMMER INSTITUTE





EFFECTS OF GENETICS AND MUTATIONS ON ACQUIRED LONG QT SYNDROME

Rebecca McFadden
Space Life Sciences Summer Research Institute
2014 JSC Pharmacology

ABOUT ME


Venice
Rotonda
Immokalee
Felda
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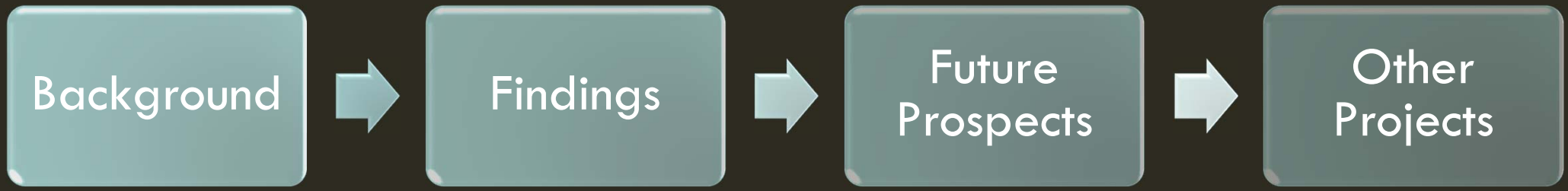
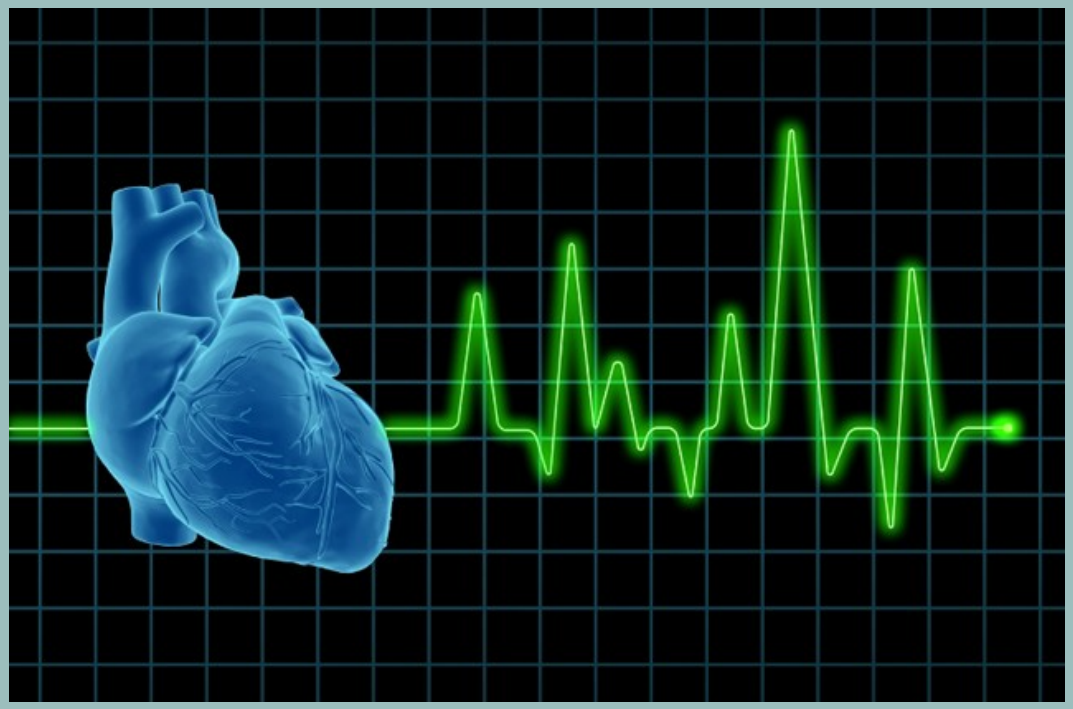
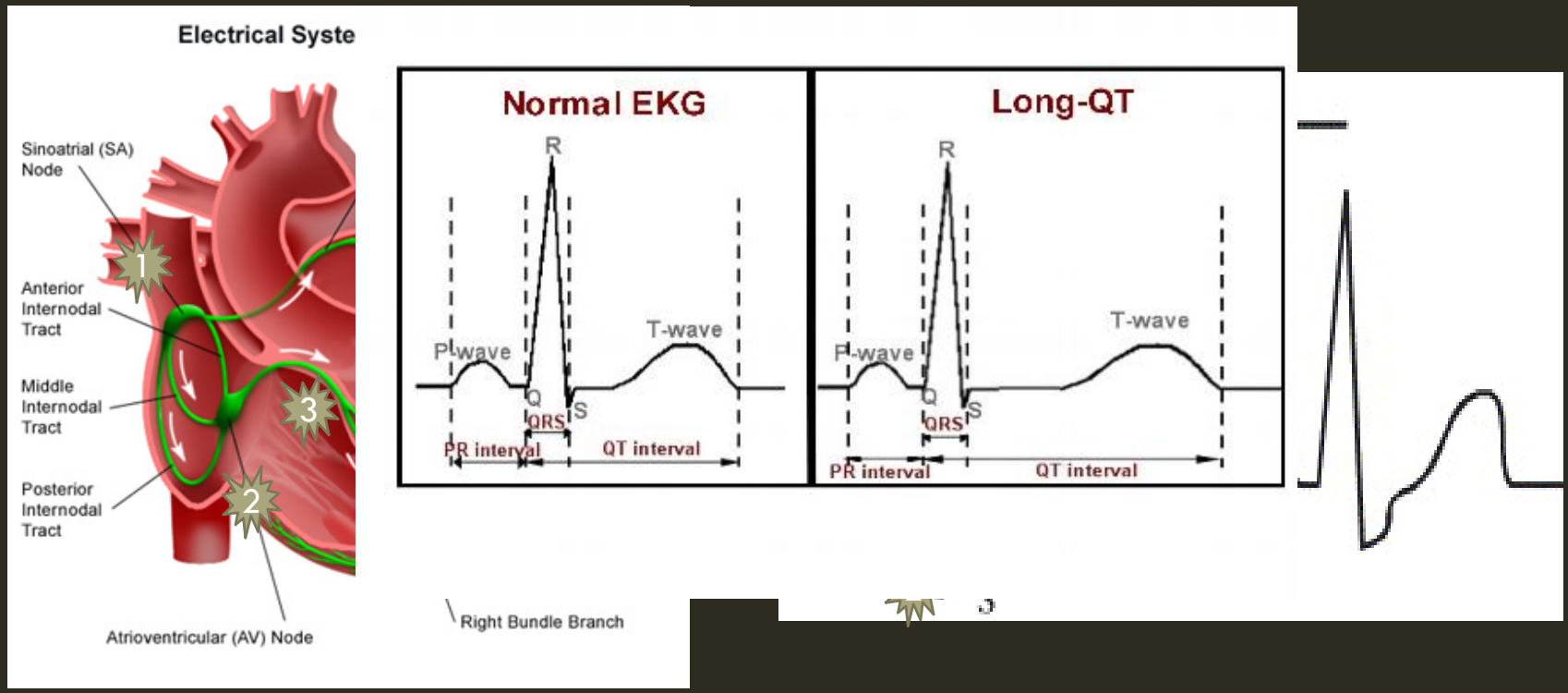
OVERVIEW





BACKGROUND

WHAT IS LONG QT?



WHAT'S THE HARM?

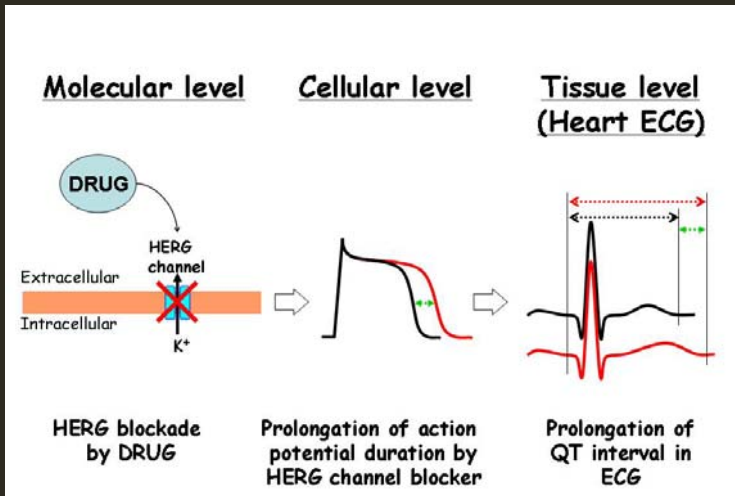
- LQTS is either inherited or acquired
  - Inherited occurs in 1/2,500 live births
    - Caused by channel gene defects
- Cannot be determined only by ECG
  - Diagnostic criteria useful, but not always accurate
- Causes 3000-4000 deaths annually in children and young adults in the US alone

	Points
Electrocardiographic findings[a]	
QTc[b]	
>480 ms	3
460–470 ms	2
450 (male) ms	1
Torsades de pointes[c]	2
T-wave alternans	1
Notched T wave in 3 leads	1
Low heart rate for age[d]	0.5
Clinical history	
Syncope[e]	
With stress	2
Without stress	1
Congenital deafness	0.5
Family history[e]	
A. Family members with definite LQTS	1
B. Unexplained sudden cardiac death below age 30 amongst immediate family members	0.5

1993 LQTS diagnostic criteria (Schwartz, 2006).

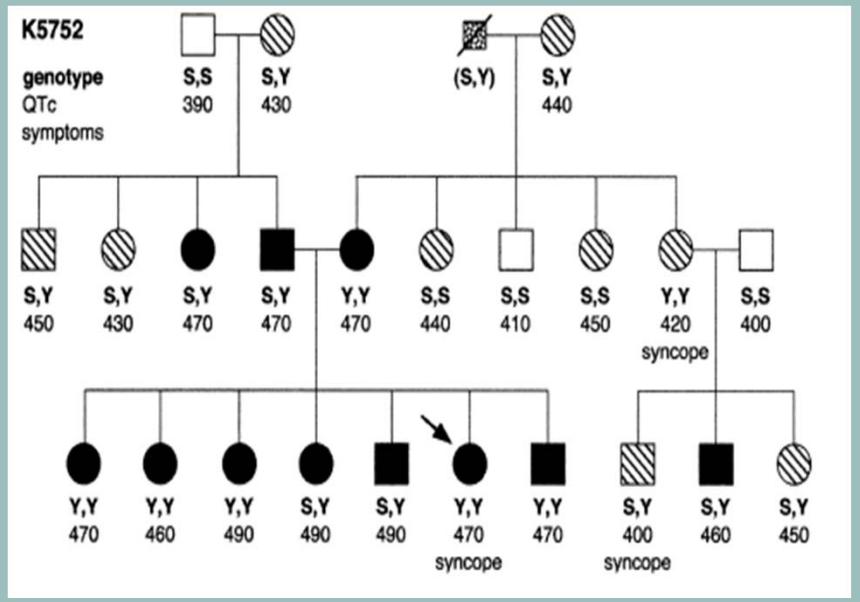
ACQUIRED LQTS

- Caused by medications
  - Can lead to Torsade de Pointes, ventricular tachycardia, ventricular fibrillation, and arrhythmia
  - Antiarrhythmics, antidepressants, antipsycotics, and antiemetics
  - Associated with 90 noncardiovascular drugs
- Most common cause of relabeling/withdrawal of market drugs in last decade
  - 1990-2001: 21 withdrawn
- Unclear why diverse compounds block HERG channels
- 2005: FDA released a Guidance for Industry
  - Drugs produced before this date have not been tested



- Currently unpredictable
  - Occurs in 1-8% of patients receiving antiarrhythmic drugs (Yang, 2002)
- Risk factors include:
  - Female gender
  - Hypokalemia
  - Hypomagnesaemia
  - Bradycardia
  - High drug concentrations
  - Heart failure

But what about genetic/inherited predisposition?

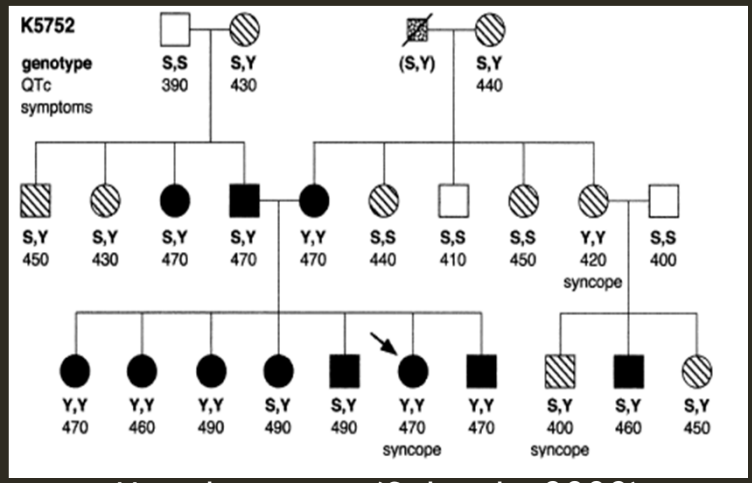

K5752
genotype
QTc
symptoms
S,S
390
S,Y
430
(S,Y)
S,Y
440
S,Y
450
S,Y
430
S,Y
470
S,Y
470
Y,Y
470
S,S
440
S,S
410
S,S
450
Y,Y
420
syncope
S,S
400
Y,Y
470
Y,Y
460
Y,Y
490
S,Y
490
S,Y
490
Y,Y
470
syncope
Y,Y
470
S,Y
400
syncope
S,Y
460
S,Y
450

FINDINGS

SILENT MUTATIONS

- 9 genotyped probands without clinically affected family members entered the study
  - 46 family members examined; none affected by LQTS on ECG
- Molecule diagnosis revealed 15 family members were gene carriers
  - This was missed by ECG and the clinical scale
  - Possible to be a gene carrier without a prolonged interval
- 13 mutations have been identified
- These individuals are predisposed to the possible occurrence of drug-induced Torsade de Pointes

SCN5A GENE



Hereditary tree (Splawski, 2002)

- Provides instructions for making sodium channels
- One patient exposed to cisapride
  - Had normal QT interval prior
  - Developed prolonged QT interval, severe bradycardia, and repetitive torsade de pointes
  - Return to normal 6 days after discontinuation
  - Due to a genetic mutation in a sodium channel
- Possesses a polymorphism more prevalent in aLQTS
  - 23 family members examined of the proband
  - 11 members carry the allele
- Knowing these could allow the identification of at-risk individuals

THE GENETIC LINK

- Acquired LQTS shares many features with congenital
  - Genetic factors may determine susceptibility
- Three main genes: KCNQ1, KCNH2, and SCN5A
  - Overall, ten associated
- Quinidine study
  - LQTS occurs in individuals who are genetically predisposed, but requires an additional stressor
- Genetic re-sequencing
  - In 31 subjects, 20 carried missense variants across a set of 79 genes
  - Further, 23% carry previously identified cLQTS genes
  - Findings suggest overlap between cLQTS and aLQTS may be greater than previously reported

FUTURE PROSPECTS

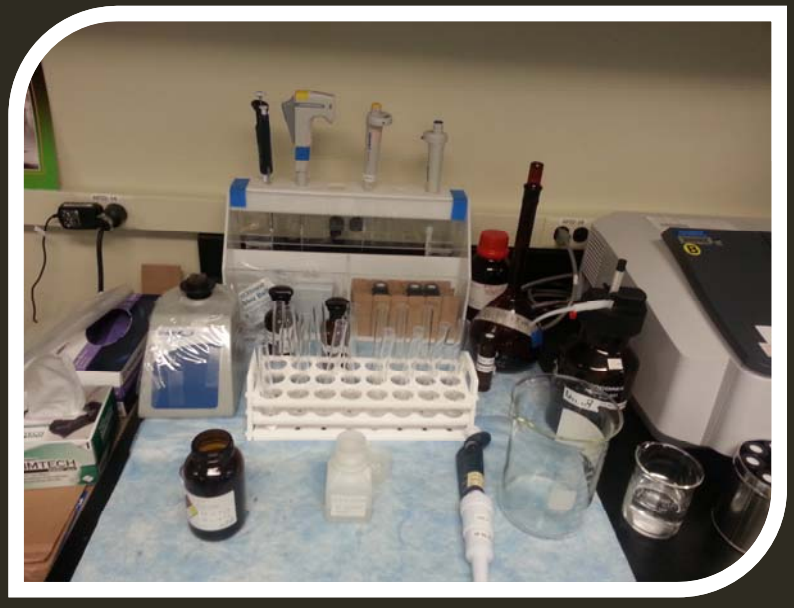
WHERE DO WE GO?

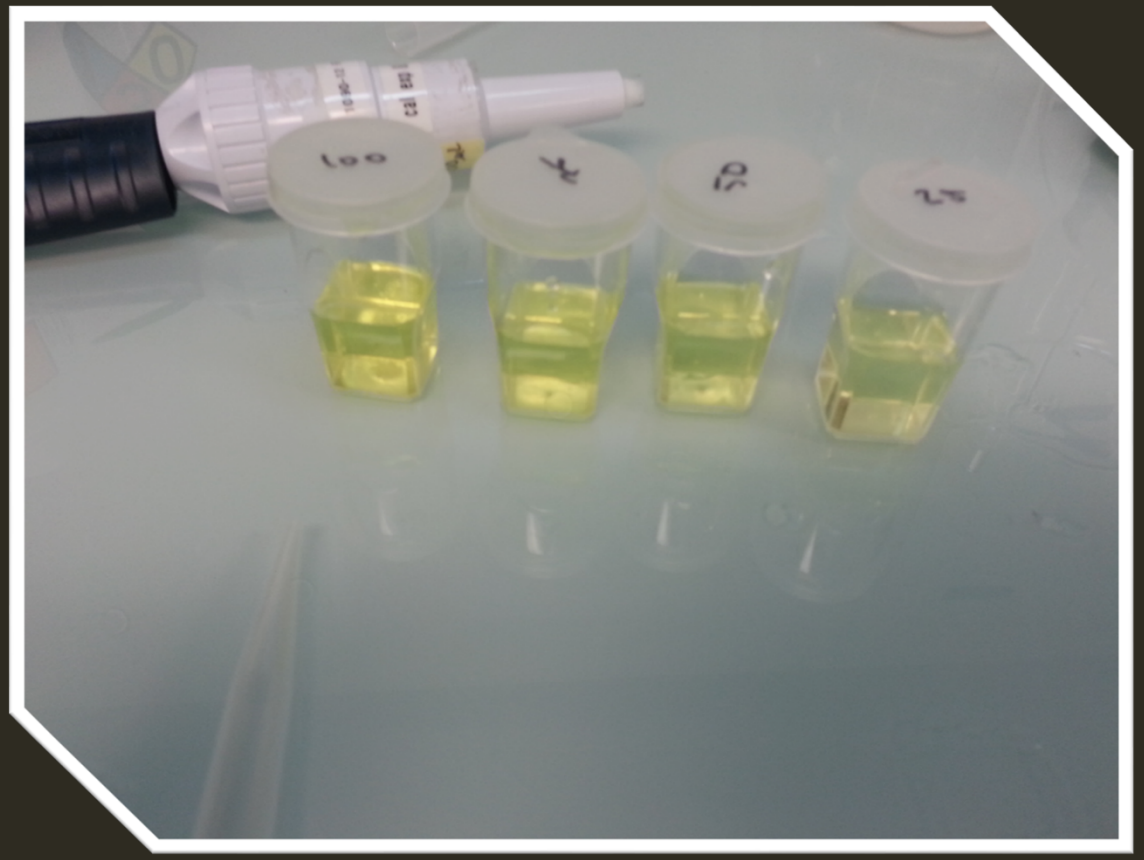
- With the proper knowledge, many of these cases are *preventable*
- Genetic screening
  - Genotyping costs need to fall
  - Genotype- based pharmacotherapy
  - More significantly robust genomic markers necessary
- A perfectly healthy individual can be a gene carrier for a lethal syndrome

Table 1. Drugs That May Cause Torsade de Pointes.*

Drugs commonly involved
Disopyramide
Dofetilide
Ibutilide
Procainamide
Quinidine
Sotalol
Bepridil
Other drugs†
Amiodarone
Arsenic trioxide
Cisapride
Calcium-channel blockers: lidoflazine (not marketed in the United States)
Antiinfective agents: clarithromycin, erythromycin, halofantrine, pentamidine, sparfloxacin
Antiemetic agents: domperidone, droperidol
Antipsychotic agents: chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide
Methadone

OTHER PROJECTS



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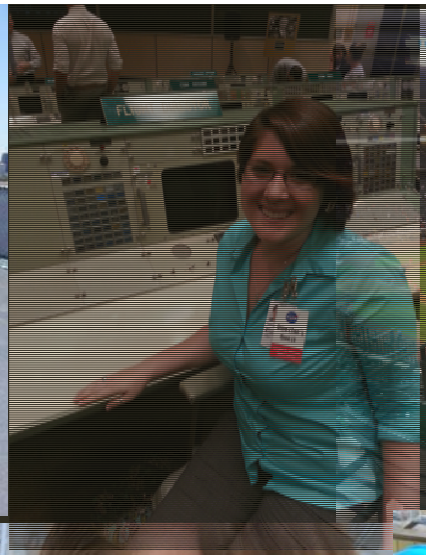
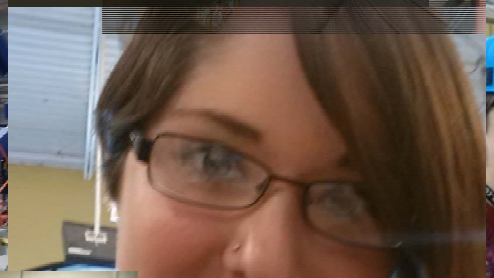



Neutral Buoyancy Laboratory
Visitors Gallery
NBL
Neutral Buoyancy Laboratory
NASA / JSC




BCM
RICE

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Jeffrey Rutz

Lauren Merkle

Ron McNeel

Rebecca McFadden

Florida Institute of Technology

rmcfadden2012@my.fit.edu

rebecca.s.mcfadden@nasa.gov