



230615 – HDIAC SME

Wearable biochemical monitoring? Very recent breakthroughs will make performance and health monitoring a nearer term reality.

Prof. Jason Heikenfeld
University of Cincinnati



Conflict of Interest Statement: Heikenfeld is a co-founder of two startups pursuing biosensor commercialization for dehydration (Hydrolabs) and interstitial fluid (Kilele Health)



Four Waves ...

◆ Major investments in technology.

◆ However, a severe knowledge gap remains between blood-based knowledge and emerging biofluids (saliva, sweat and interstitial fluid).

1st Wave (20th century)

Sample to the Lab

2nd Wave (20th → 21st)

Lab to the Sample

3rd Wave (emerging)

Wear the Lab

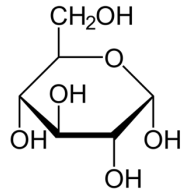
4th Wave (frontier)

Implant the Lab

3rd Wave: Status

Most are incremental advances on decades old sensing paradigms.

Directly sensing chemical analytes is needed.



...but how hard is it to move beyond glucose?

✓ Specific!
✗ But... only n=1 (glucose).

NON-SPECIFIC

NON-SPECIFIC

NON-SPECIFIC

How many things can make your heart rate change?



How Hard Can it Be? Very Hard!

🔹 2nd Wave lab to the user, glucose.



🔹 3rd Wave, wear the lab, glucose. After decades and \$100's millions of dollars...



🔹 Two decades and only one success? How do we move beyond just glucose and *not have to wait 2 more decades...*

Roadmap for Moving Beyond Just Glucose...

Instead of just another review of *who has done what*, today we will focus the conversation through four lenses:

(1) **Physiology:** which biofluid for continuous monitoring?

(2) **Sensors:** what sensor chemistry is most promising?

(3) **Wearables:** what device format is preferred for DOD?

(4) **Applications:** how should the DOD choose their foci?

What Biofluids To Focus On?

Blood and urine
are well studied!



Saliva is
diagnostically
like sweat.



Tears not
compelling.




2nd Wave (20th → 21st)



Lab to the Sample

3rd Wave (emerging)



Wear the Lab

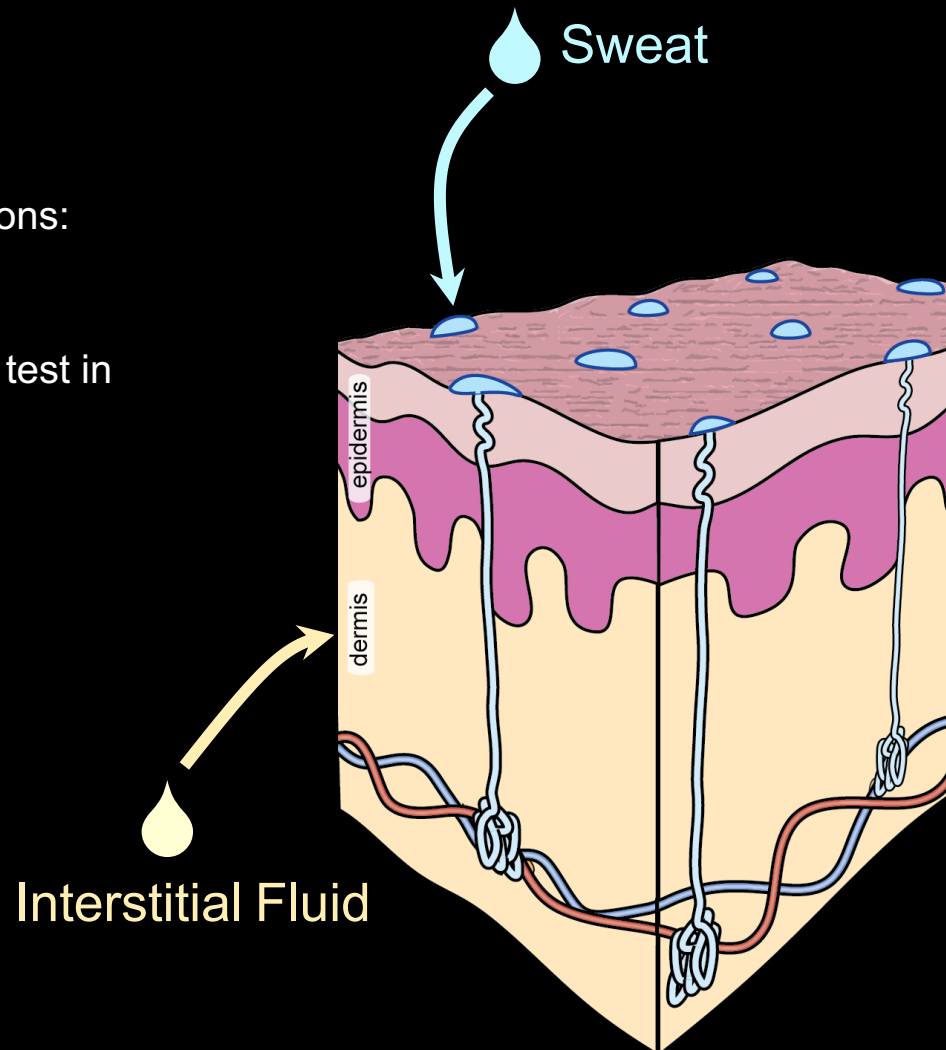
Sweat or Interstitial Fluid?

💧 Most research has been on sweat for two reasons:

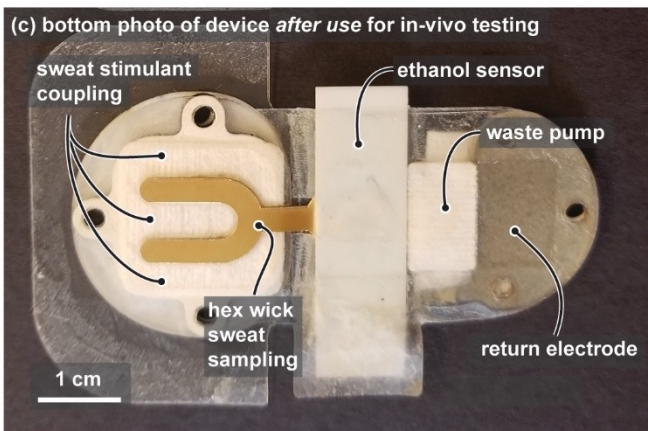
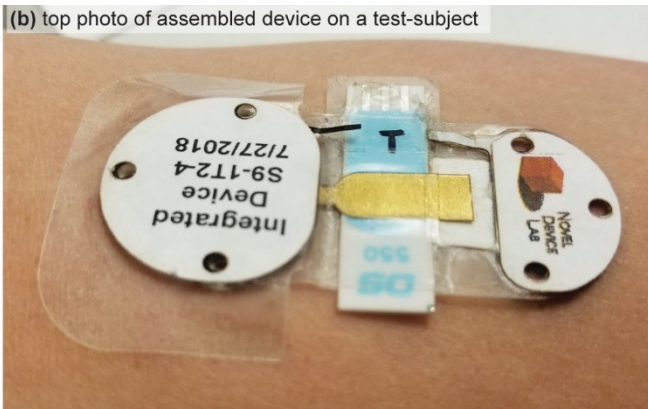
(1) It's a hot attention-grabbing topic.

(2) It's non-invasive and easier for researchers to test in their labs than interstitial fluid.

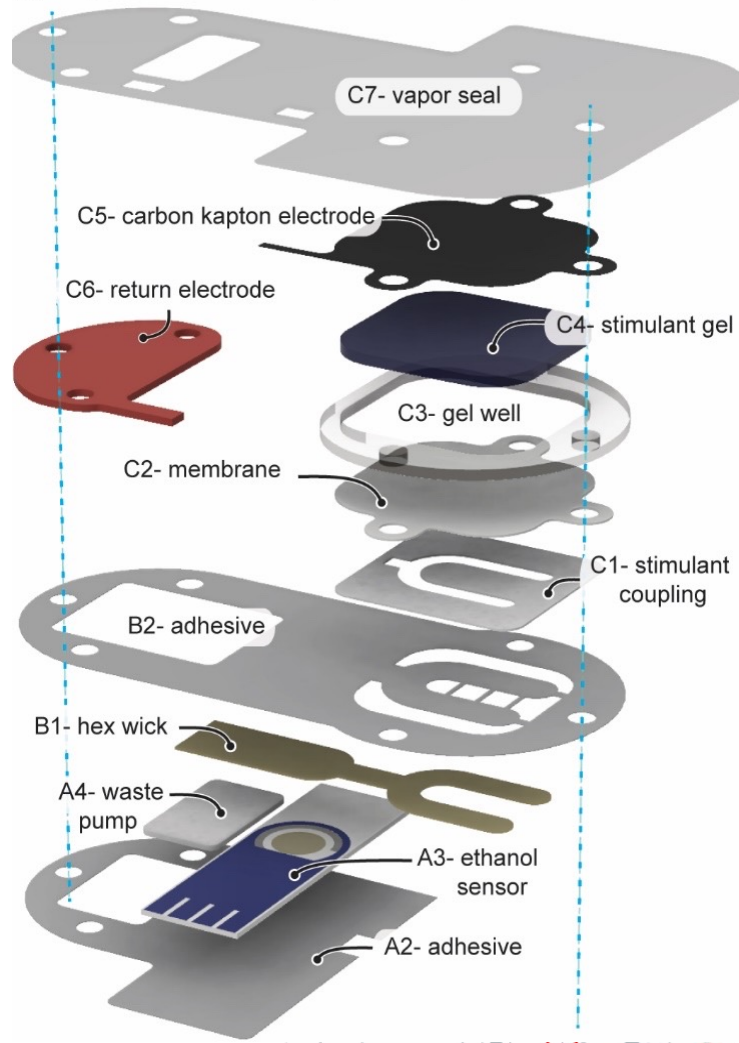
Lets review a 'false start' with sweat...

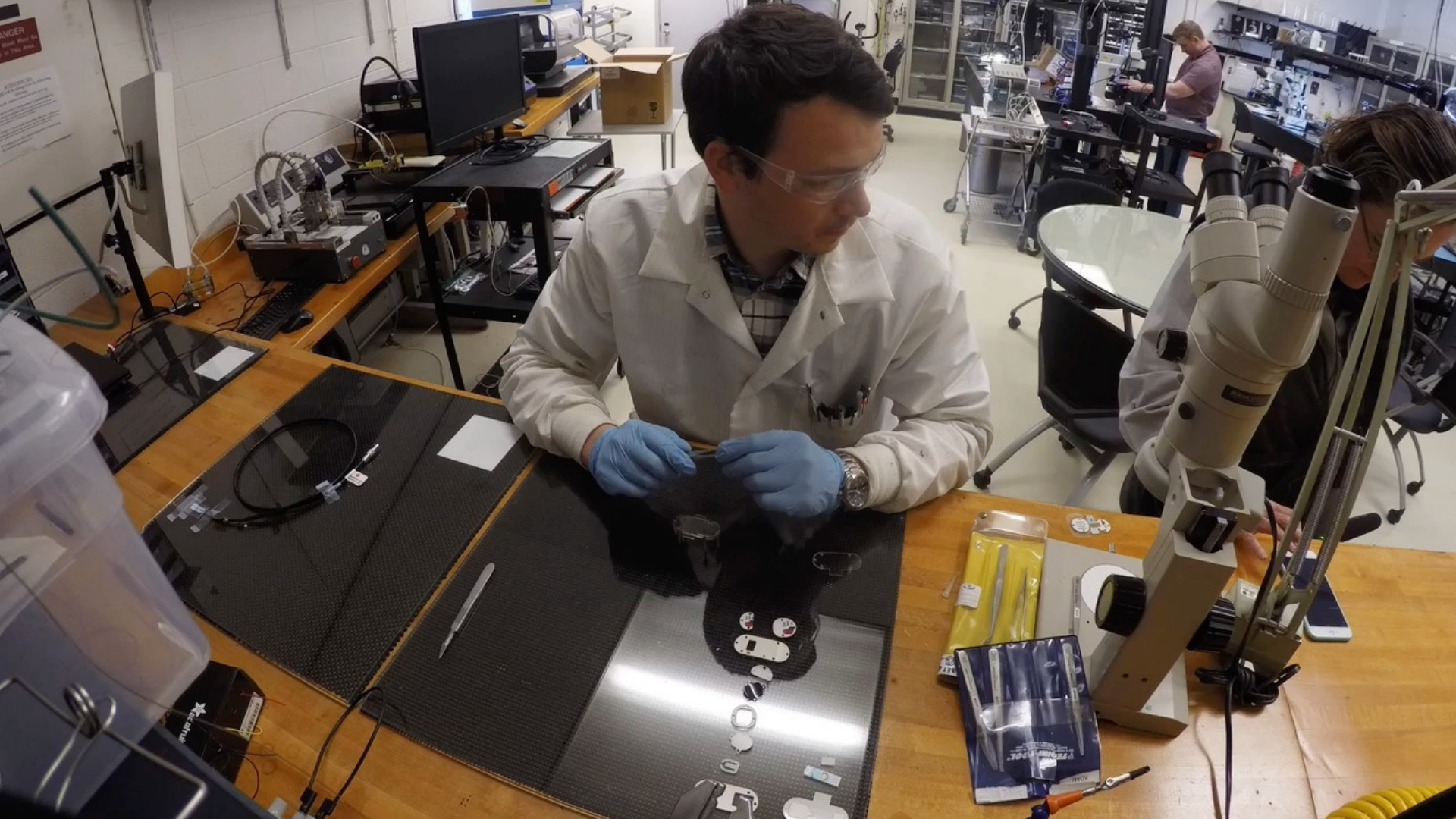


Prime Example: Our Sweat Patch

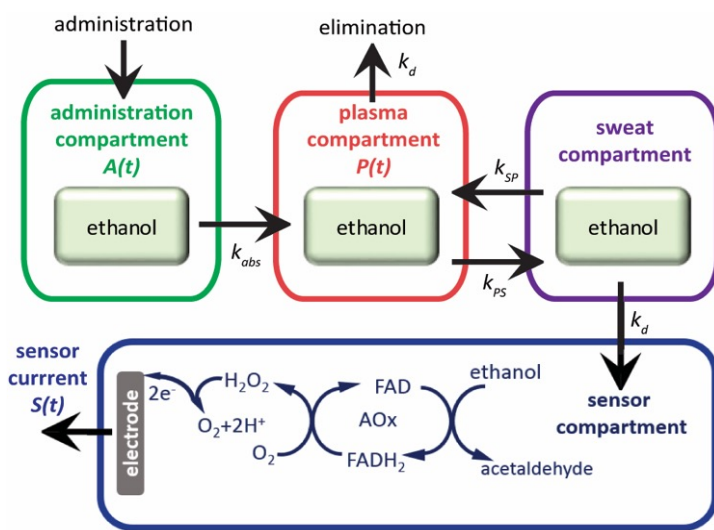
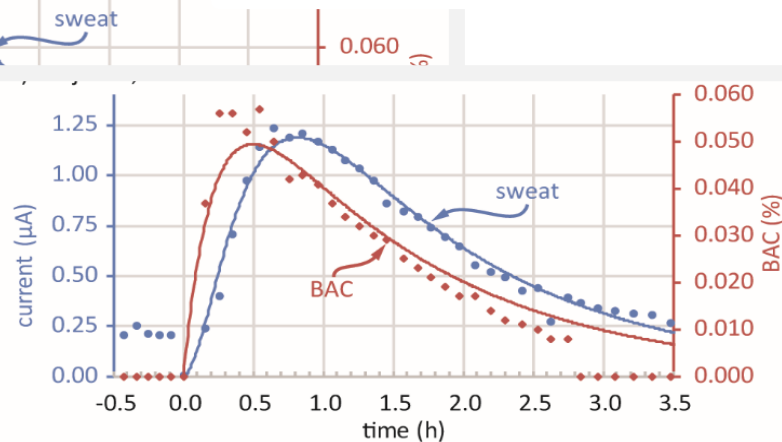
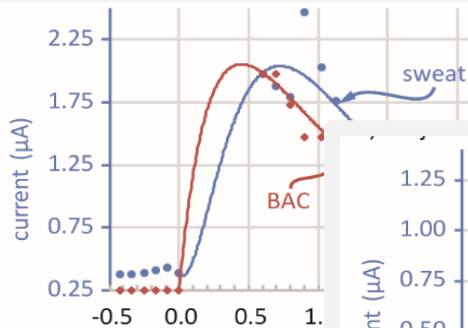
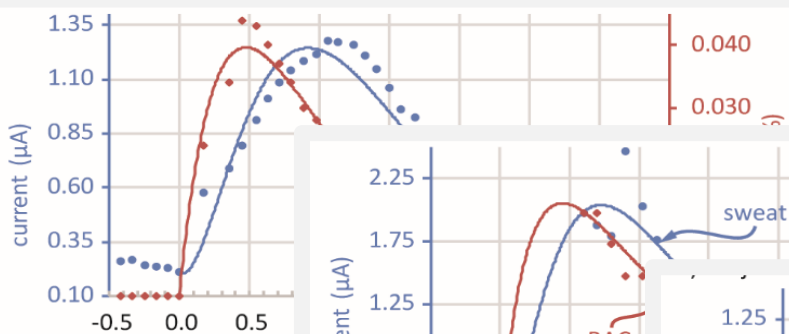
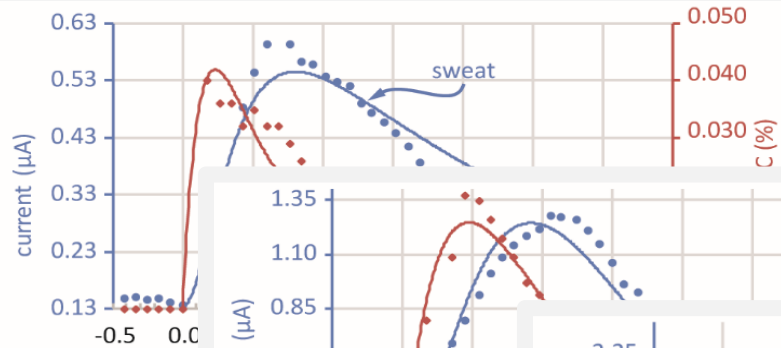


(a) integrated device stack up (all materials)





Enzymatic Sweat Ethanol Sensing...

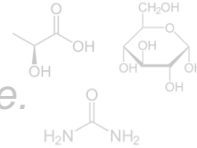


We Got Ahead of Ourselves with a Technology First Approach...

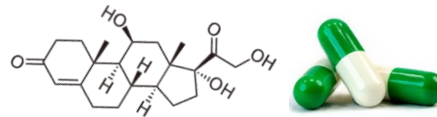
Electrolytes – Na⁺ is proportional to sweat rate (active secretion), K⁺ similar to blood.
Not competitive.

Na⁺, K⁺, pH, Cl⁻

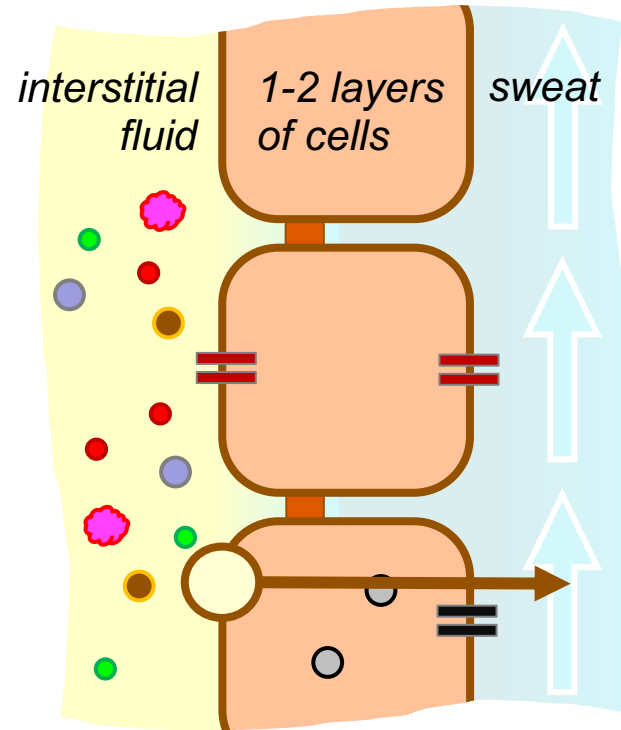
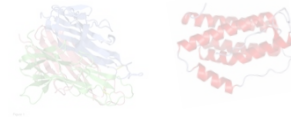
Metabolites – lactate not useful (gland metabolism), glucose tracks blood but ~100X dilute.
Not competitive.



Small molecules – lipophilic analytes are 1:1 w/ blood (hormones, drugs).



Proteins? – ratios are accurate but ~1000X dilute
Not competitive.



Sweat has utility but it is limited and demo's have been complicated hero-experiments...

What About Interstitial Fluid?

💧 It's a much simpler picture...

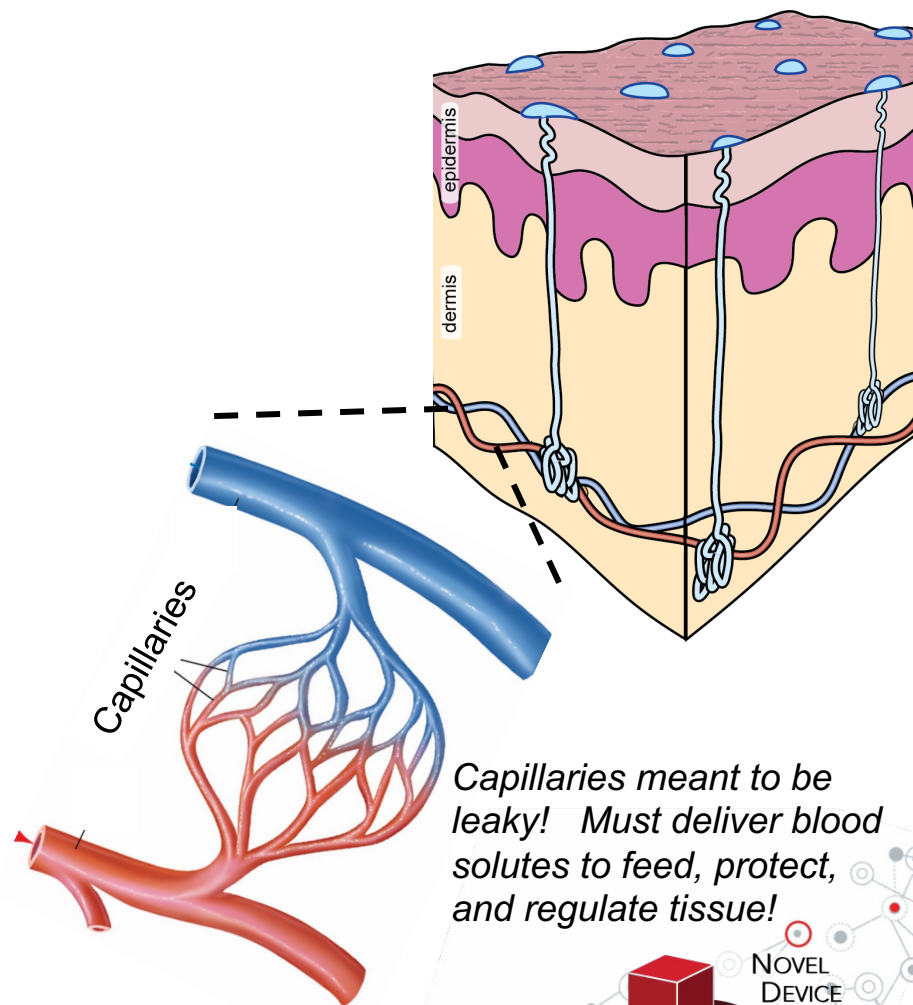
Electrolytes - Correlate well with blood ✓

Metabolites – Correlate well with blood ✓

Small molecules – Correlate well with blood ✓

Proteins – Correlate with blood up to 10's kDa ✓

Interstitial fluid IS broadly useful and device demo's are PROVEN for glucose monitors!



Capillaries meant to be leaky! Must deliver blood solutes to feed, protect, and regulate tissue!

Roadmap for Moving Beyond Just Glucose...

Instead of just another review of *who has done what*, today we will focus the conversation through four lenses:

(1) **Physiology**: which biofluid for continuous monitoring?

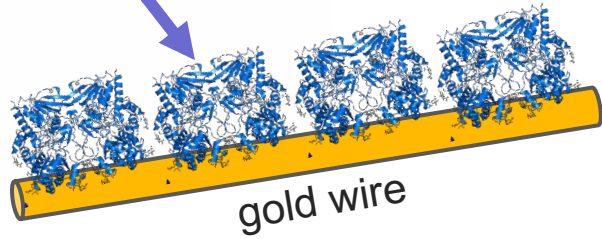
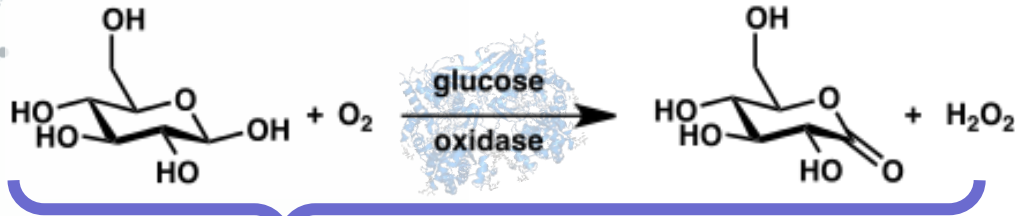
INTERSTITIAL FLUID

(2) **Sensors**: what sensor chemistry is most promising?

(3) **Wearables**: what device format is preferred for DOD?

(4) **Applications**: how should the DOD choose their foci?

How Glucose Monitors Work (Enzymatic Sensors)



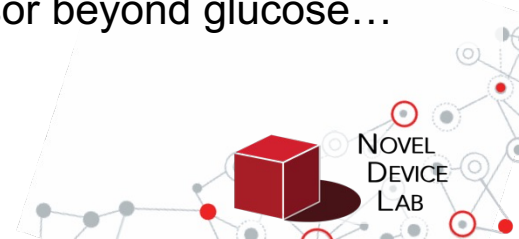
💧 Pain-free and tiny gold wire inserted ~3 mm into the skin

💧 So what is holding up moving beyond glucose?



ITS NOT THE DEVICE

Needles? Microneedles? Sweat? Implanted? It's all irrelevant without a platform sensor beyond glucose...



So What is REALLY Holding Up Moving Beyond Glucose?

- (1) Enzymes typically FOUND in nature (hard to create)
- (2) Enzymes ONLY work for very-high concentration targets like glucose (mM).



mM (milli-molar) glucose, ethanol, lactate, etc.

μ M (micro-molar) most drugs, amino acids, etc.

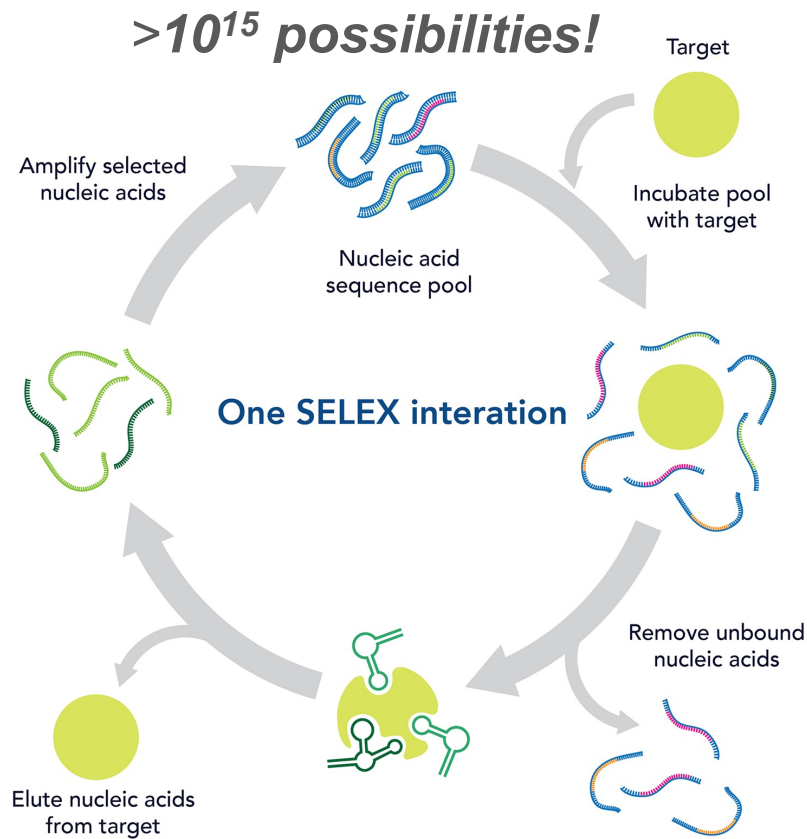
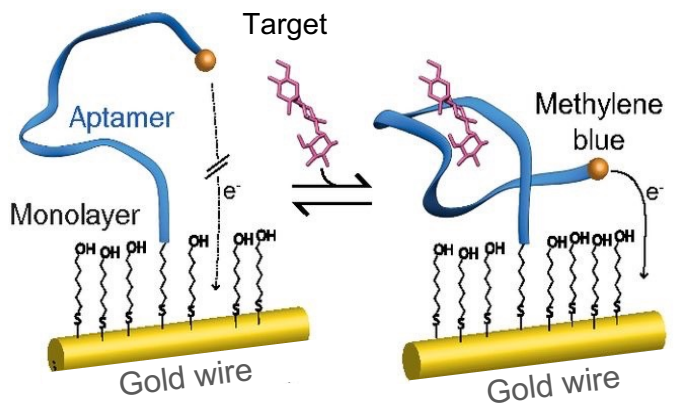
nM (nano-molar) hormones and other important small targets

pM (pico-molar) most protein targets that are important

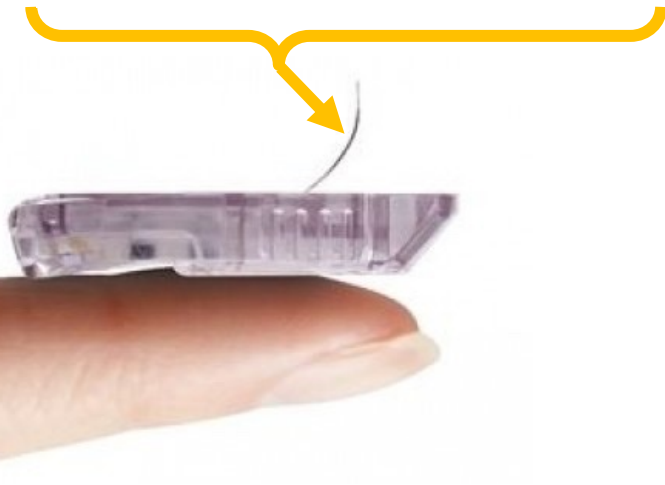
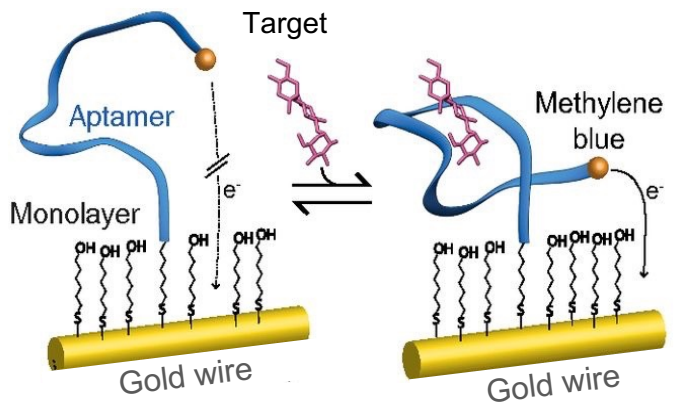
So what other options?

10's of thousands of journal articles on in-vitro (beaker) demonstrated sensors and only ONE other sensor platform beyond enzymes shown to work broadly in-vivo (in body).

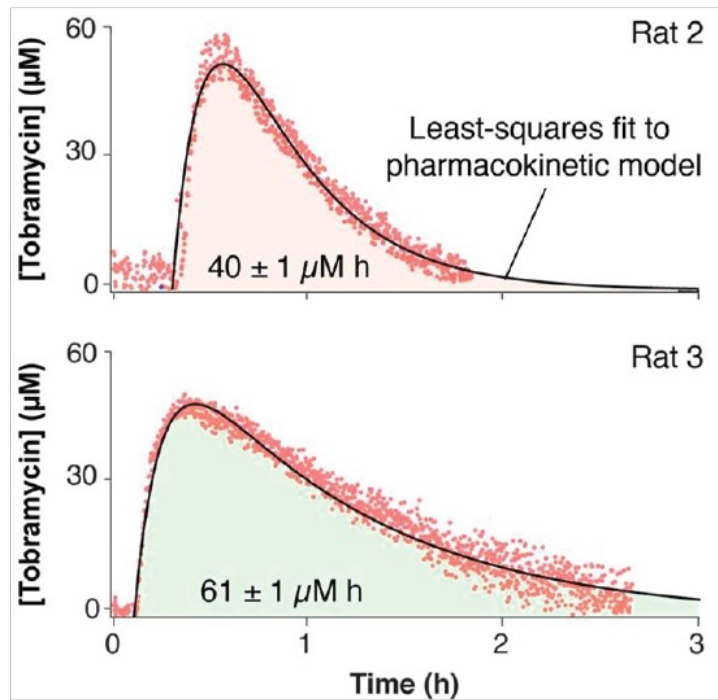
Electrochemical Aptamer Sensors



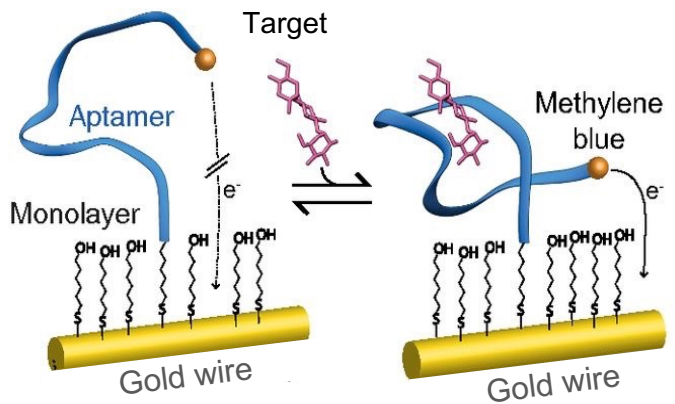
Electrochemical Aptamer Sensors



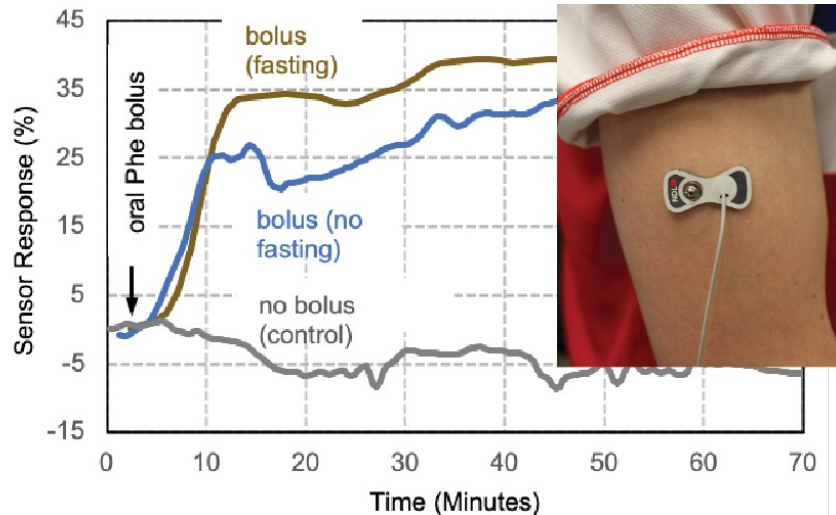
◆ Demonstrated for DOZENS of targets in-vivo (rats)!



Electrochemical Aptamer Sensors



◆ Our group has demonstrated in human data as well!

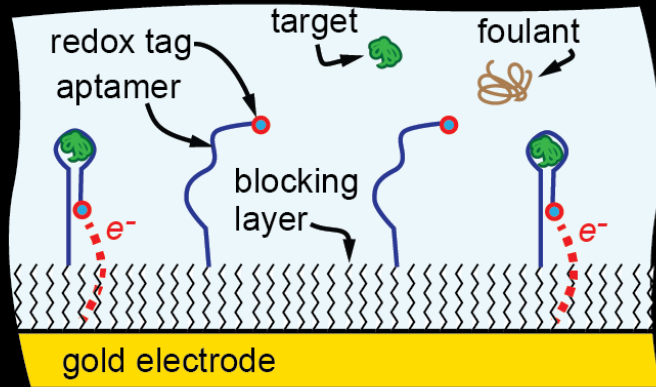


But demos have been limited to

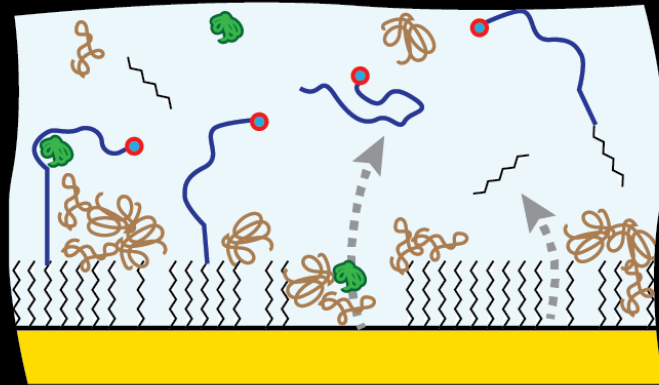
- hours: *need days to weeks!*
- μM concentrations: *need nM to pM!*

The Deficiency with Aptamer Sensors...

In a beaker, room temp, clean solution...
PERFECT HARMONY



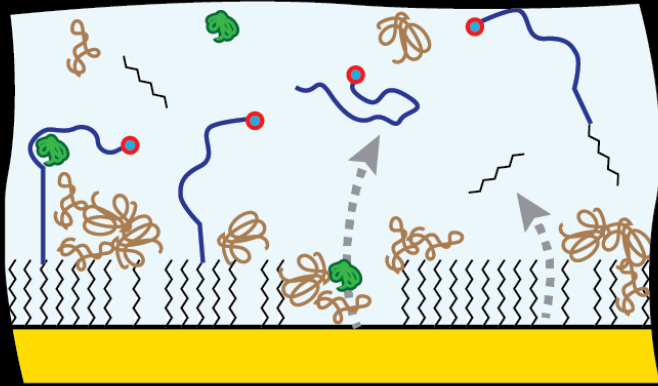
In the body, its messy and hotter (body temp)...
CHAOS...



The Historical Deficiency with Aptamer Sensors...

In the body, its messy
and hotter (body temp)...

CHAOS...



If it only lasts 6 hours...

\$100 for
2 weeks

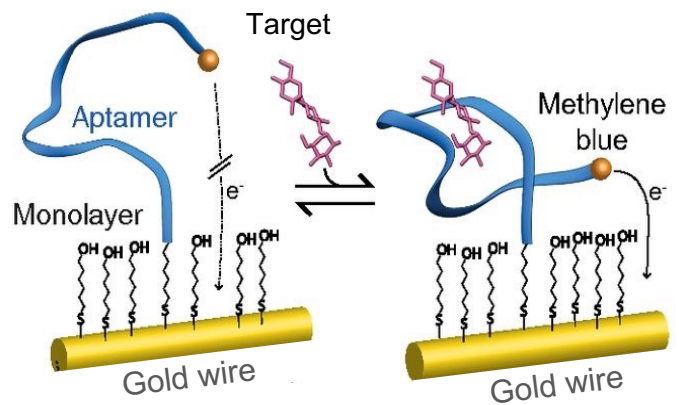
**\$5000 for
2 weeks**



**Also
might as
well go
back to
this.**



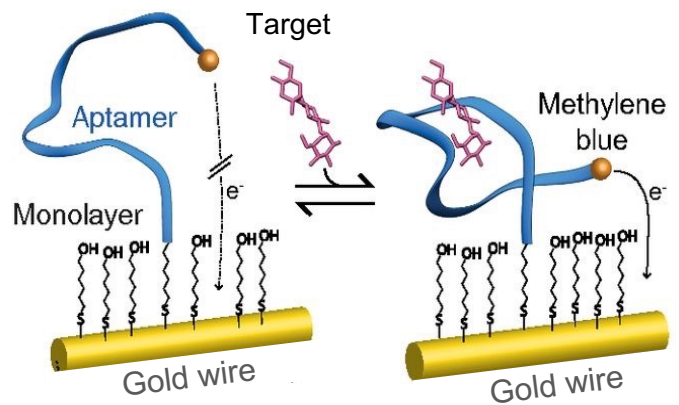
Recent Breakthroughs in Longevity and Detection Limits



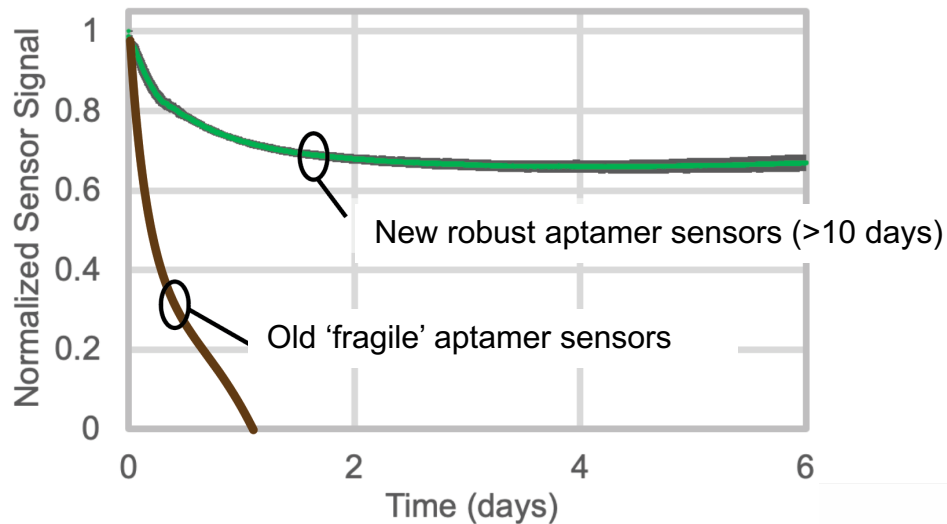
Standing on the shoulders of Plaxco, Kippen, White, Arroyo, Soh, and others...



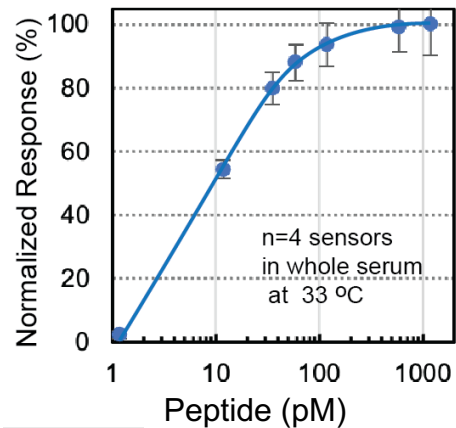
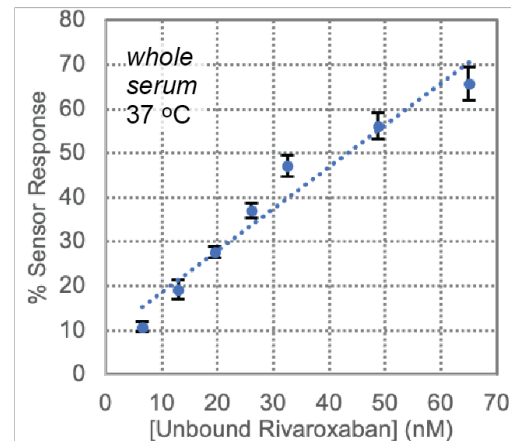
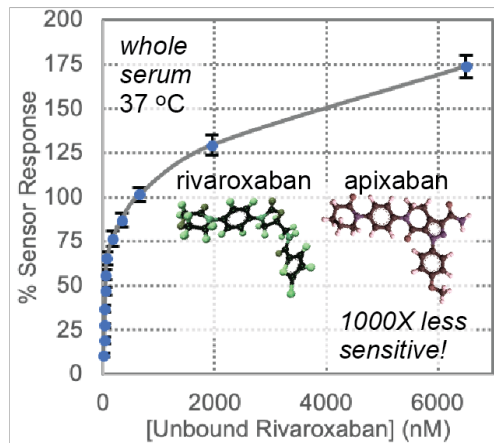
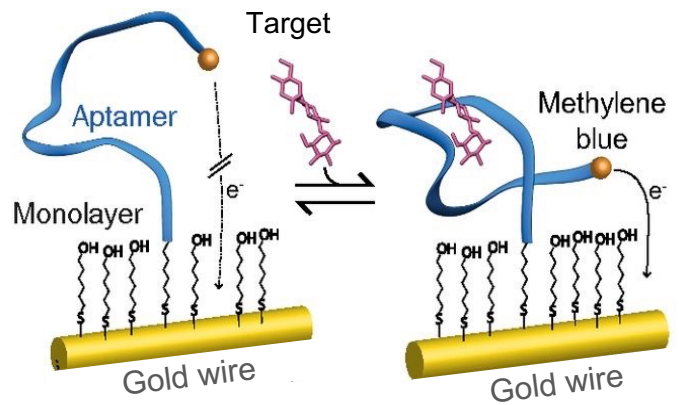
Recent Breakthroughs in >10 day Longevity



- (1) Energetically stabilize the monolayer chemistry
- (2) Add charged antifouling chemistry



Recent Breakthroughs in Detection Limits (nM and pM!)



Roadmap for Moving Beyond Just Glucose...

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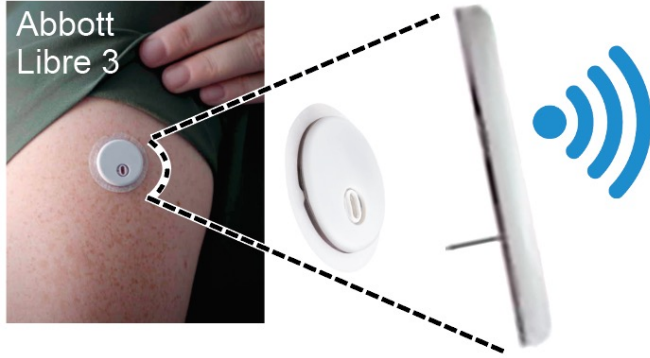
(2) **Sensors**: what sensor chemistry is most promising? *APTAMER SENSORS*

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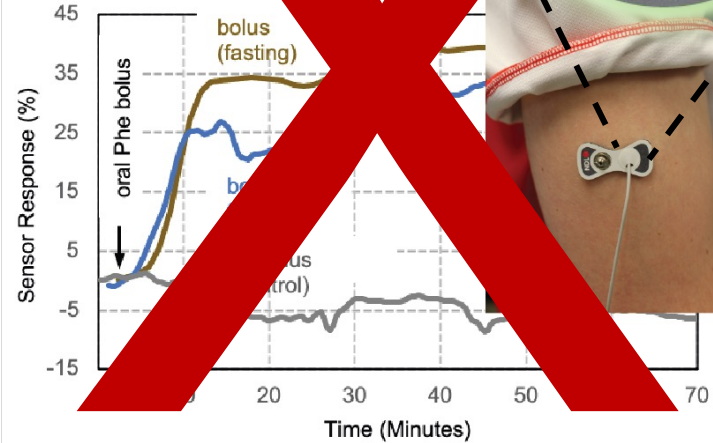
Needles vs. Microneedles

5 mm deep single needle



vs.

0.7 mm deep microneedle arrays



- (1) painless insert for 9/10 users... *and for DOD pain is not issue.*
- (2) 5 mm depth is more reliable: *there is a REASON for it.*
- (3) The devices are beautiful! \$25 manufacturing cost, fully disposable, 2 week use!

For most applications
what unresolved problem
are microneedles solving?

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- | | |
|------------------------------------------------------------------|------------------------------------|
| (1) Physiology: which biofluid for continuous monitoring? | <i>INTERSTITIAL FLUID</i> |
| (2) Sensors: what sensor chemistry is most promising? | <i>APTAMER SENSORS</i> |
| (3) Wearables: what device format is preferred for DOD? | <i>1 NEEDLE LIKE ABBOTT</i> |
| (4) Applications: how should the DOD choose their foci? | |

Continuous Monitoring, What Analytes to Target?

Physical performance
and recovery during
intense training

Cognitive
performance and
fatigue – not easy...

Chem/bio warfare
agent pre-symptom
detection

ADVICE #1 - need to better define DOD needs → then find best analyte to meet the need.

- its been mainly engineers talking to DOD personnel – need to bring in doctors!

ADVICE #2 – leverage sensor development that is targeting civilian applications.

- unless you want to pump in \$100's millions of dollars yourself for 10 years...

Continuous Monitoring, What Analytes to Target?

ADVICE #2 – leverage sensor development that is targeting civilian applications.

- unless you want to pump in \$100's millions of dollars yourself for 10 years...



KILELE HEALTH

*Bending the Curve for Chronic
Condition Management*

Chronic diseases

\$3.8T (20% of GDP)

(Fierce Healthcare, 2019 data)

75% of direct health care spend

(Fightchronicdisease.org, 2019 data)

Finish with Three Major Conclusions

(1) Most of us have now figured out, the generally preferred biofluid is ISF:

- for continuous measure, it is generally superior in accuracy to alternatives
- the device part is arguably 'a solved problem'



(2) Aptamer sensors are the most believable route forward and 'ready for prime time'

- *>1 week longevity is a major breakthrough that was missing before (else just do POC tests)*

(3) Deeper discussion on DOD's most pressing unmet needs is merited, and bring in MDs.

**THANK YOU
HDIAC + OUR
R&D SUPPORT!**