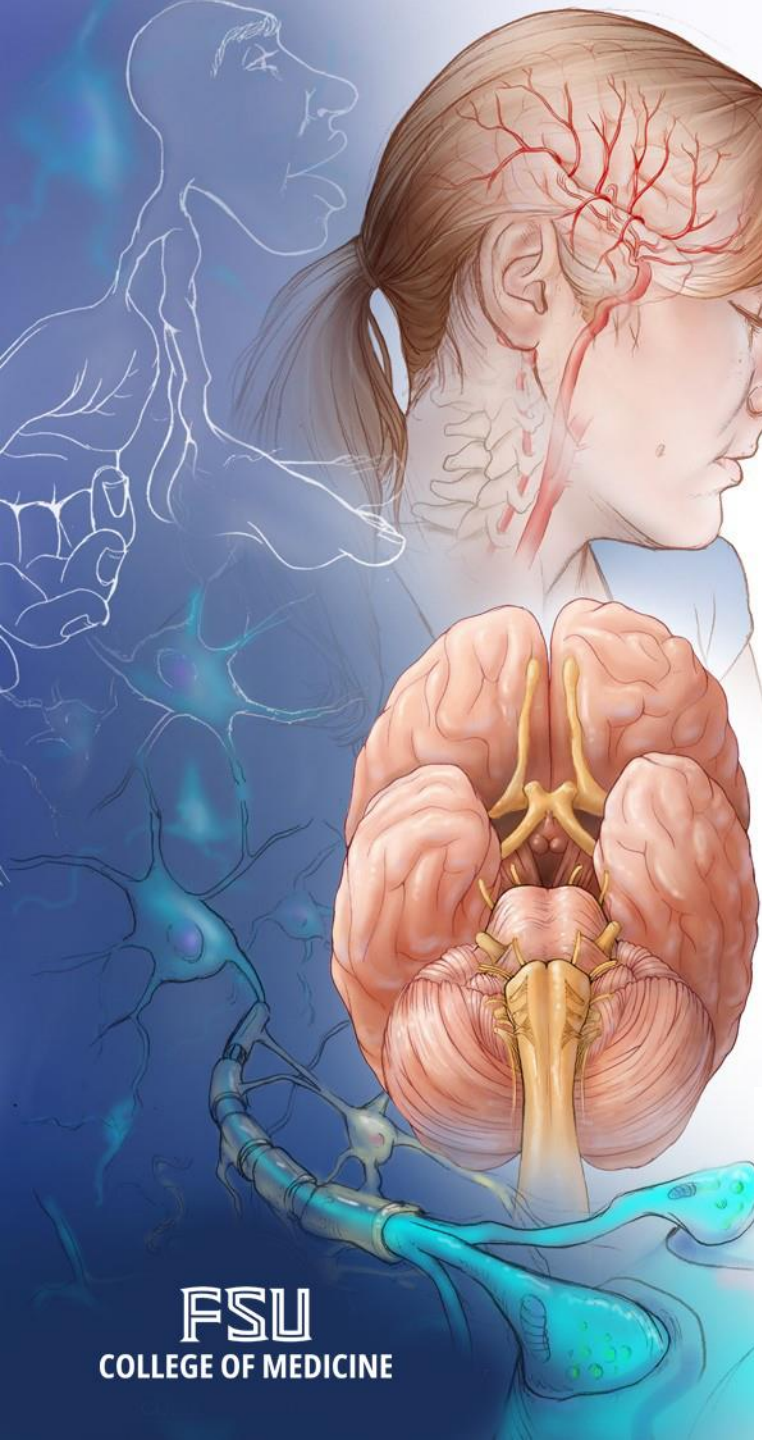

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Reverse Translation in Animals and Cell Models: Methods to Accelerate Therapeutic Development and Mechanisms

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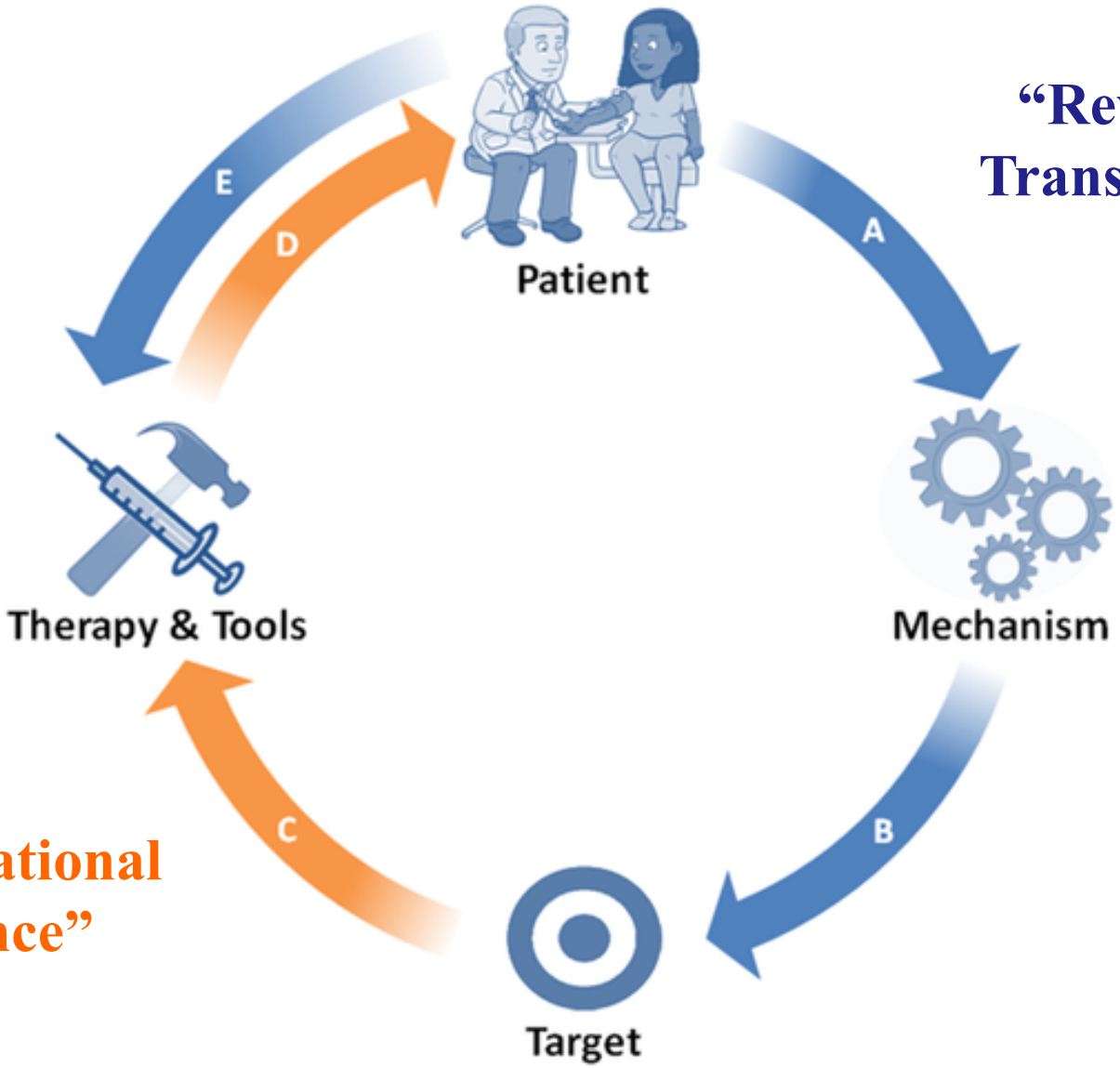
Florida State University College of Medicine

Objectives

- Define and contrast the concepts of translation and reverse translation.
- Articulate some of the advantages and disadvantages of animal models and non-animal alternatives.
- Provide examples to illustrate the value of reverse translation.



"Reverse Translation"

"Translational Science"

John A. Wagner (2017), Patient-Centered Reverse Translation. Clin. Pharmacol. Ther., 103: 168-170. doi: 10.1002/cpt.902

Sushruta (~7th or 6th century BC) was a physician in ancient India- the "Father of Indian Medicine".

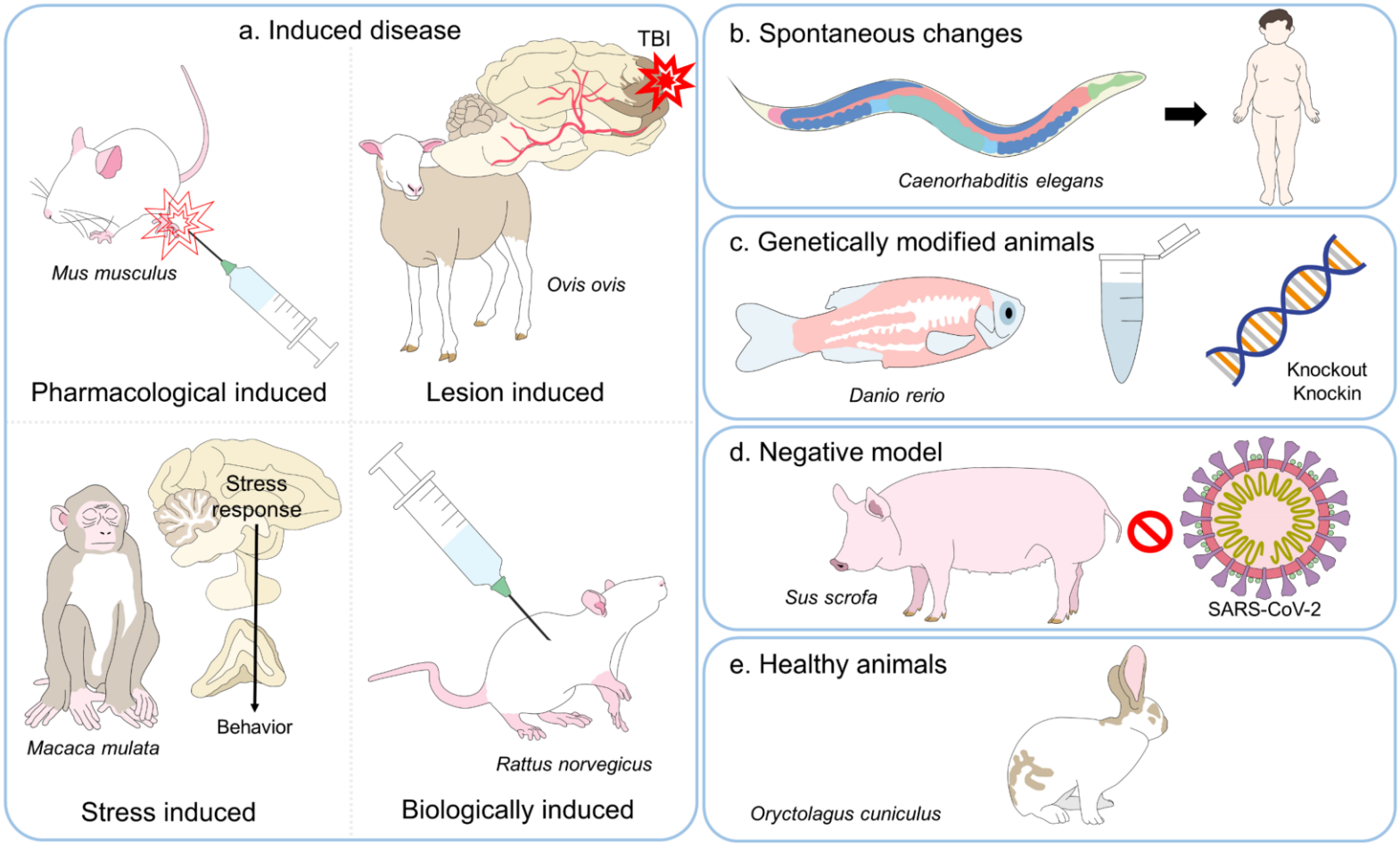
He described and classified diabetes, known as Madhumeha (honey-like urine), in his medical "textbook", the Sushruta Samhita.

He identified diabetes by observing the sweet taste and ability of the urine to attract ants.

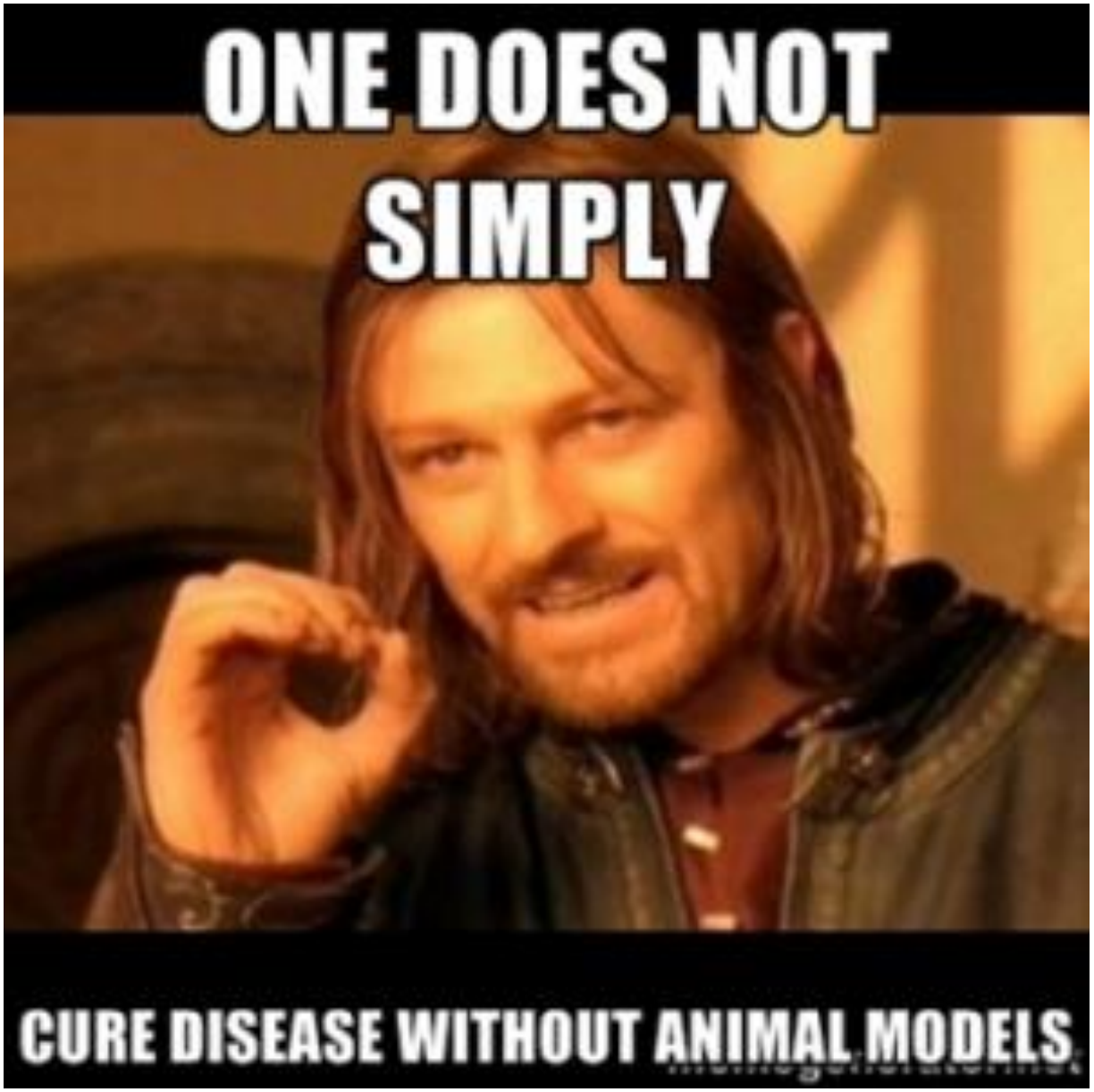
Examples of Reverse Translation

- Patient-Driven Rapid Translation
  - viral diagnostics during COVID
- Genomics
  - patient data used to generate new hypotheses and enable precision medicine
- Drug Repurposing
- Understanding therapeutic “failures”
  - especially patient and response heterogeneity

Testing in animal models has been a major cornerstone of translational medicine



Domínguez-Oliva et al., 2023, Animals 13, 1223.


ONE DOES NOT
SIMPLY
CURE DISEASE WITHOUT ANIMAL MODELS

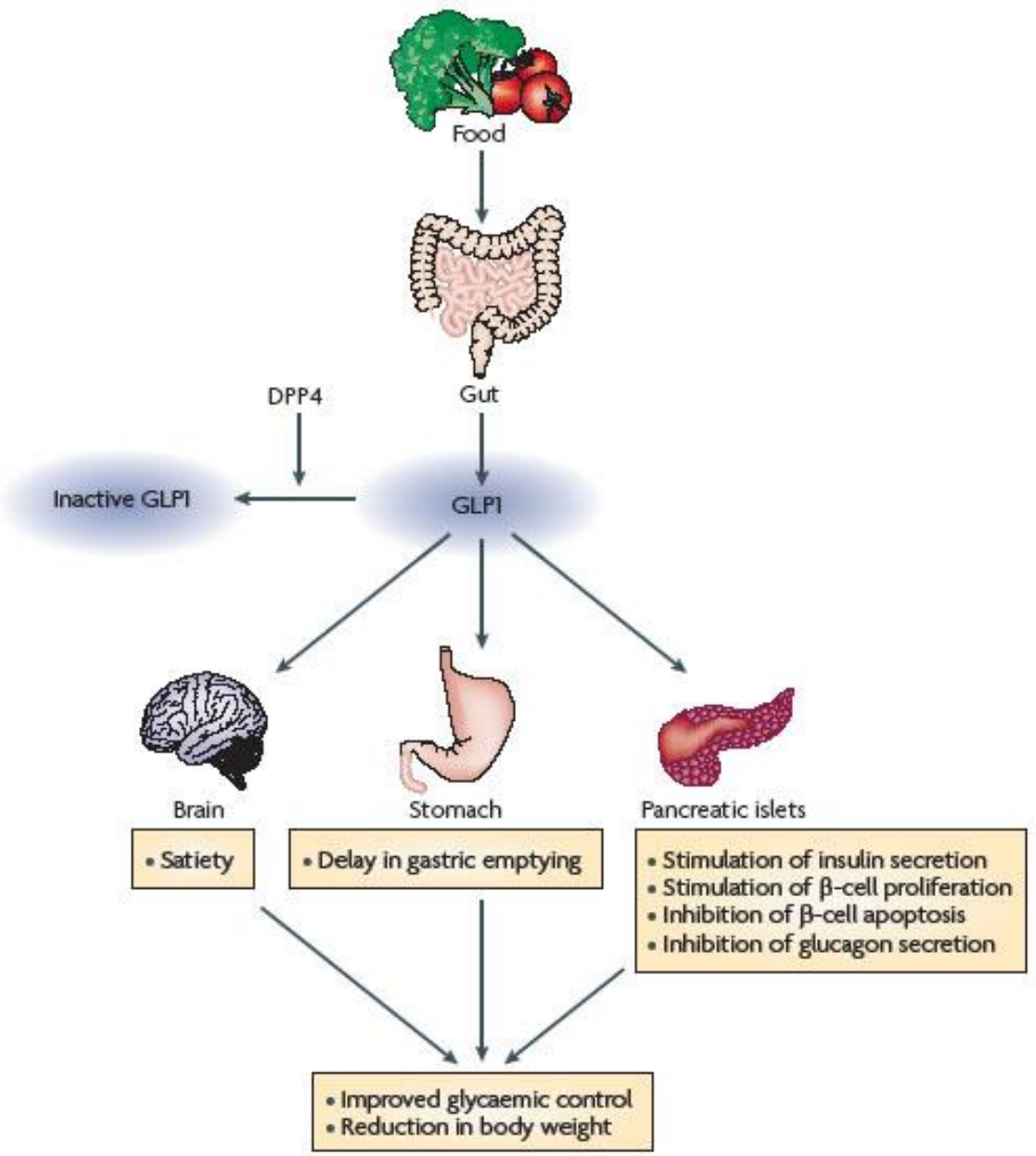
However, there have been shifts in favor of non-animal alternatives.

Considering the high failure rates of forward translation from animal models to human application, a paradigm shift is welcome.

However, the assumptions, reliability and representativeness of non-animal alternatives also has major limitations and needs more investigation – and enthusiasm to these approaches cannot become the basis for completely replacing animal testing.

System	Advantages	Disadvantages
Animal Models	Represent whole-body mechanisms and reactions Many well-established models already exist	Not all biological responses can be translated to humans Genetic and environmental / life history variability is often poorly represented Many translational failures have now been documented
Cell Culture	Able to target specific mechanisms Relatively inexpensive and high throughput	Physical and chemical complexities of target organs not included Disease progression usually cannot be assessed
3D Cultures and/or Organoids	Represents 3D human-derived tissue Tends to have increased reproducibility as compared to other in vitro systems	Costly and time-consuming Small cell and restricted viability Does not include vasculature or immune cells/systems Still in the “Wild West” stage of unique methods amongst labs
Microphysiologic Systems	Can closely mimic tissue microenvironments Can study interactions amongst some cell types Possible to examine dynamic response characteristics	Inter-organ effects are not represented Usually missing circulating cells Minor differences in system design can produce very different outputs and outcomes
Invertebrate Models	Small size, simpler anatomy and brief life cycle Robust genetic perturbation methods Cost effective and reduced ethical concerns	Underdeveloped and sometimes poorly conserved organ systems Metabolism and physiological responses are typically quite different from humans
In silico Models	Low cost and time-effective Absence of ethical concerns Can quickly identify new therapeutic candidates	Unable to accurately replicate in vivo conditions We do not know what we do not know
Artificial Intelligence / Machine Learning	Hypothesis-independence Has promise to add in early detection of disease and treatment-response Can exploit robust data analytic approaches	How to train it? Garbage in, garbage out – it’s only as good as the data and training it receives

An Example: GLP-1



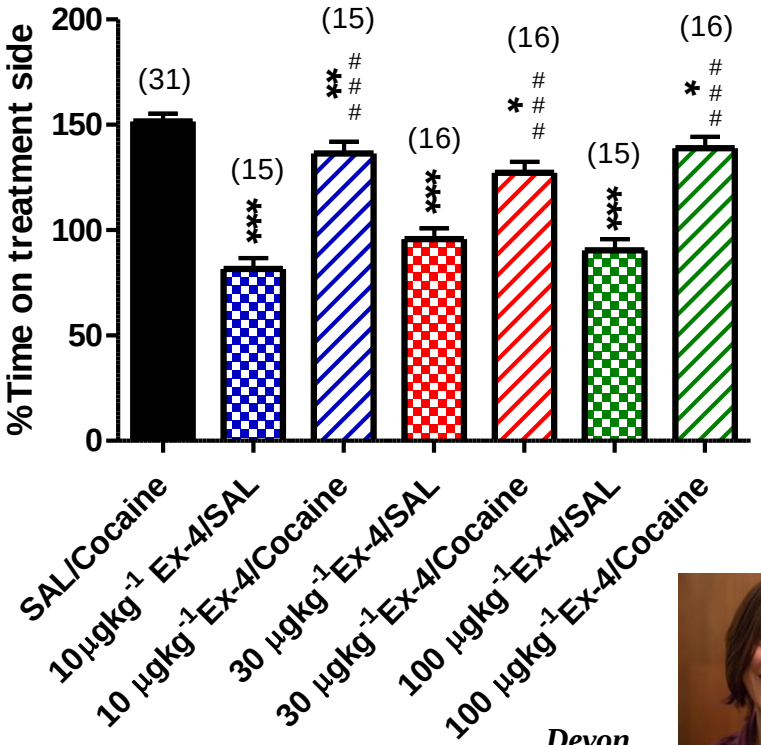
- The incretin GLP-1 is produced by cleavage of proglucagon in intestinal L cells in response to food intake.
- GLP-1 potentiates insulin secretion, inhibits glucagon secretion, slows gastric emptying, and reduces appetite. It is very short-lived – metabolized immediately.
- GLP-1 is also produced in the NTS and its central actions are important for food reward – via brain GLP-1Rs.

Ahren 2009, Nature Rev Drug Discovery

GLP-1R and Drug Reward

GLP-1R activation reduces the reinforcing effects of cocaine (and alcohol, nicotine, and opioids) in animals.

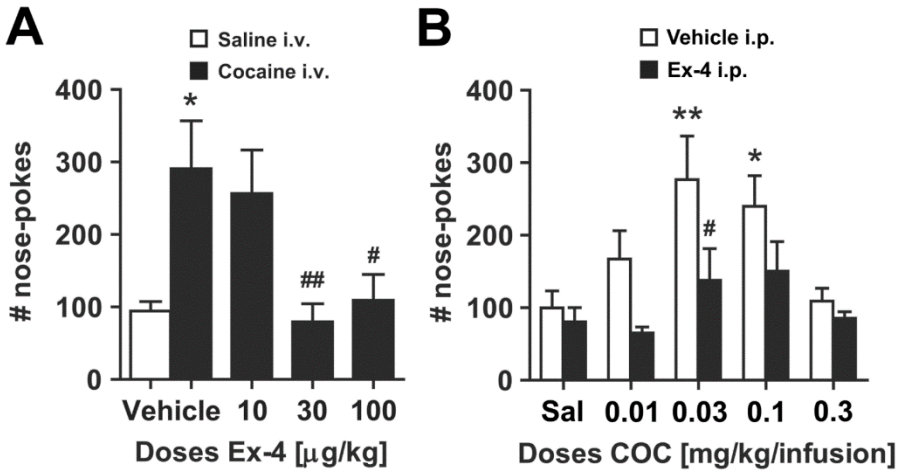
Place Conditioning



Mol Psychiatry. 2013 18:961-2

Devon Graham

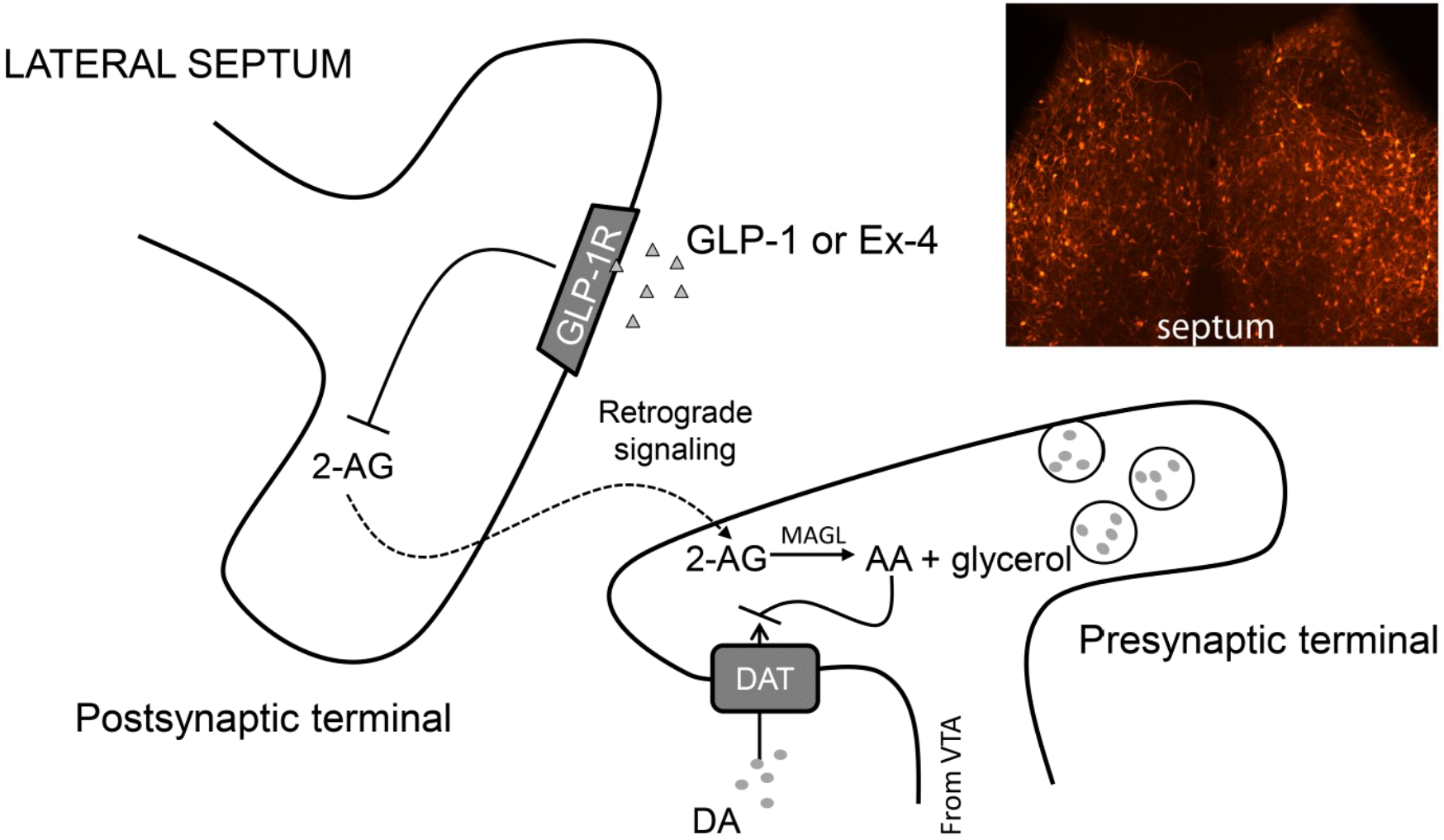
Self-Administration



Physiol Behav. 2015 149:262-8

Anders Fink-Jensen University Hospital of Copenhagen, Denmark

GLP-1R-mediated retrograde regulation of DA uptake in the lateral septum



Reddy, et al (2016), Transl Psychiatry, 6(5):e809. doi: 10.1038/tp.2016.86.
Graham, et al., 2020, J Comp Neurol 528:2445-2470. doi: 10.1002/cne.24905

GLP-1R Agonists for Substance Use Disorders?

Exenatide once weekly for alcohol use disorder investigated in a randomized, placebo-controlled clinical trial

Mette Kruse Klausen,[1,2] Mathias Ebbesen Jensen,[1,2] Marco Møller,[1] Nina Le Dous,[1] Anne-Marie Østergaard Jensen,[1] Victoria Alberte Zeeman,[1] Claas-Frederik Johannsen,[1] Alycia Lee,[3,4] Gerda Krog Thomsen,[5] Julian Macoveanu,[1] Patrick MacDonald Fisher,[5] Matthew Paul Gillum,[6] Niklas Rye Jørgensen,[2,7] Marianne Lerbæk Bergmann,[8] Henrik Enghusen Poulsen,[2,9] Ulrik Becker,[10] Jens Juul Holst,[2,6] Helene Benveniste,[11] Nora D. Volkow,[12] Sabine Vollstädt-Klein,[3,4] Kamilla Woznica Miskowiak,[1,2,13] Claus Thorn Ekstrøm,[14] Gitte Moos Knudsen,[2,5] Tina Vilsbøll,[2,15] and Anders Fink-Jensen[1,2]

JCI Insight 2022;7(19):e159863

1) attenuated fMRI alcohol **cue reactivity** in the ventral striatum and septal area.
2) Lowered dopamine transporter availability
3) reduced **heavy drinking days** and total alcohol intake in a **subgroup of obese patients.**

JAMA Psychiatry

RCT: Once-Weekly Semaglutide in Adults with Alcohol Use Disorder

POPULATION

14 Men, 34 Women

Non-treatment-seeking adults meeting criteria for alcohol use disorder

Mean (SD) age, 39.9 (10.6) y

SETTINGS / LOCATIONS

1 US academic medical center

INTERVENTION

48 Participants randomized and analyzed

24 Semaglutide
Once-weekly semaglutide

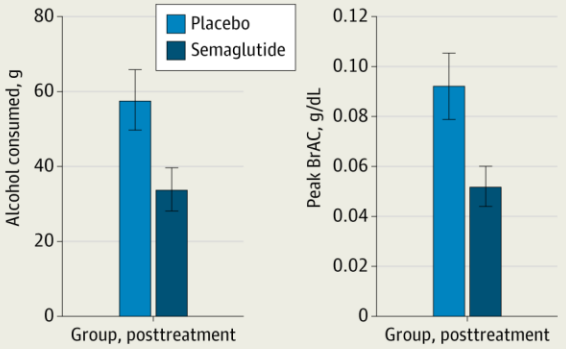
24 Placebo
Placebo injections

PRIMARY OUTCOME

Estimated alcohol consumed over 120 min during laboratory self-administration (estimated alcohol consumed in grams and peak breath alcohol concentration [BrAC] in g/dL)

FINDINGS

Among participants consuming alcohol in a laboratory session following 8 wk of treatment, those in the semaglutide group drank significantly less alcohol than those in the placebo group



Mean (SD) alcohol consumed: Semaglutide: 33.62 (20.72) g; placebo: 57.19 (28.15) g
Mean (SD) peak BrAC: Semaglutide: 0.052 (0.029) g/dL; placebo: 0.092 (0.046) g/dL
Effect sizes: Alcohol consumed: β, −0.48; 95% CI, −0.85 to −0.11; *P* = .01; peak BrAC: β, −0.46; 95% CI, −0.87 to −0.06; *P* = .03

Hendershot CS, Bremmer MP, Paladino MB, et al. Once-weekly semaglutide in adults with alcohol use disorder: a randomized clinical trial. *JAMA Psychiatry*. Published online February 12, 2025. doi:10.1001/jamapsychiatry.2024.4789

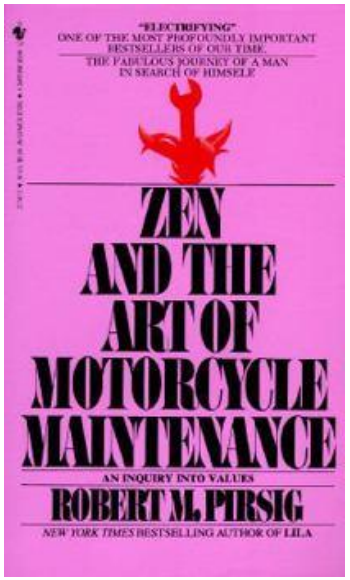
Key finding: Semaglutide decreased heavy drinking days

Zen and the Art of Cyclical Science

The original animal model data in GLP-1s and reward was very translational – it had considered dosing, duration, and some obvious aspects of drug-taking history.

But now we can appreciate additional complexities in how multiple biological, psychological, and pharmacological system interact.

Once we understand the complexities, we can rationally design tools for repair and prevention.



Mixtures, Poly-Exposures and Complex Cumulative Exposures

- This is where leaning into Reverse Translation can really, really help!
- We cannot model all exposures in the laboratory – whether in animals, cells, organs-on-chips or *in silico*.
- We must have real-world data on which combinatorial and cumulative exposures to emphasize.

Bioecological Center for Rural Children's Health

Formerly EPA-G2023-STAR-C1

- Focuses on identifying and mitigating the interactive and cumulative health consequences of chemical and non-chemical stressors in children.

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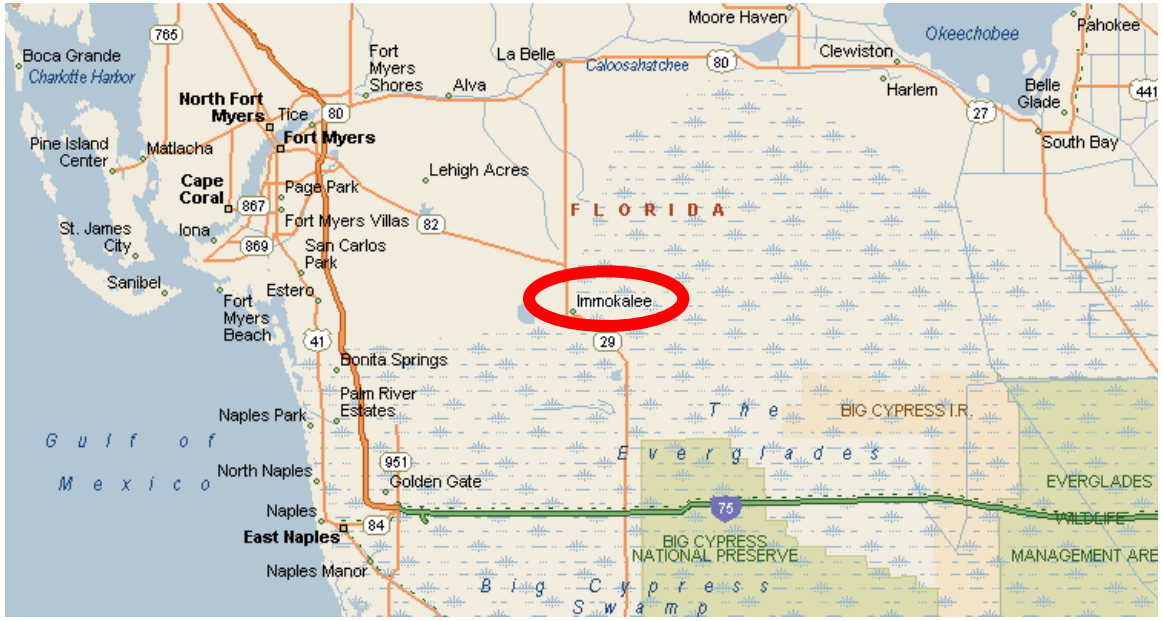

CENTER for CHILD STRESS & HEALTH
FLORIDA STATE UNIVERSITY
COLLEGE OF MEDICINE

We operate a Health Education Site in Immokalee, as well as a resource and research center focused on toxic stress (Dr. Javier Rosado).

Bioecological Center for Rural Children's Health

- **Level of the child/family** - longitudinal birth cohort study in order to document the exposures of children in a farmworker community (Immokalee) to **chemical (pesticides, metals, etc) and non-chemical (trauma, psychosocial) stressors.** Hypothesis: these stressors pathologically interact to alter biobehavioral development and negatively affect childhood and future health.
- **Cumulative impact assessment** that considers multiple processes (biophysical, built, health and healthcare, residential segregation) **at the zip code level across the state of FL**. Use machine learning and AI after merging health data (i.e. medical records) and publicly-available information around water quality, air quality, climate change, and socio-economic factors.
- Use a **participatory framework** to increase community engagement and empowerment.
- Reverse translate to mechanism – with knowledge of which exposure combinations produce the most negative outcomes.

A Simple Proposal

Reverse translation in developmental neurotoxicology represents a worthwhile shift in research framing.

Let’s encourage moving from the traditional "bench-to-bedside" approach to an explicitly cyclical process where observations from the clinic inform and drive research in the lab.

This will further bridge the gap between basic research and clinical applications, leading to better prevention and evidence-based treatments.


"That's all Folks!"