

Research Update

From Biomedical Research to Preclinical Models to Clinical Trials

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EDMONTON · ALBERTA · CANADA



“Investments and Opportunities”

For more specific information on FPWR research and clinical trials, go to www.fpwr.org/prader-willi-syndrome-research/research-webinars/

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Working Toward an Independent Future



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REQUESTS FOR FUNDING

FUNDED RESEARCH



Strategic Programs

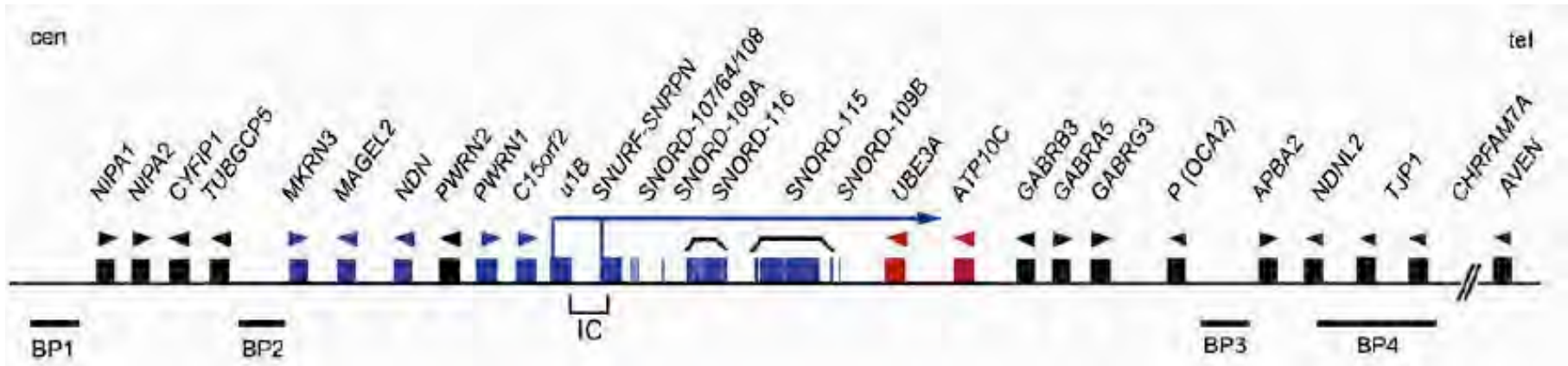
- 1: Program for *PWS gene activation* research
- 2: Program for *PWS gene* research
- 3: Program for *appetite and obesity* research
- 4: Program for *mental health* research
- 5: Program for *therapeutics in PWS*
- 6: Investments for the future



1) *PWS gene activation*

Can PWS genes be re-activated?

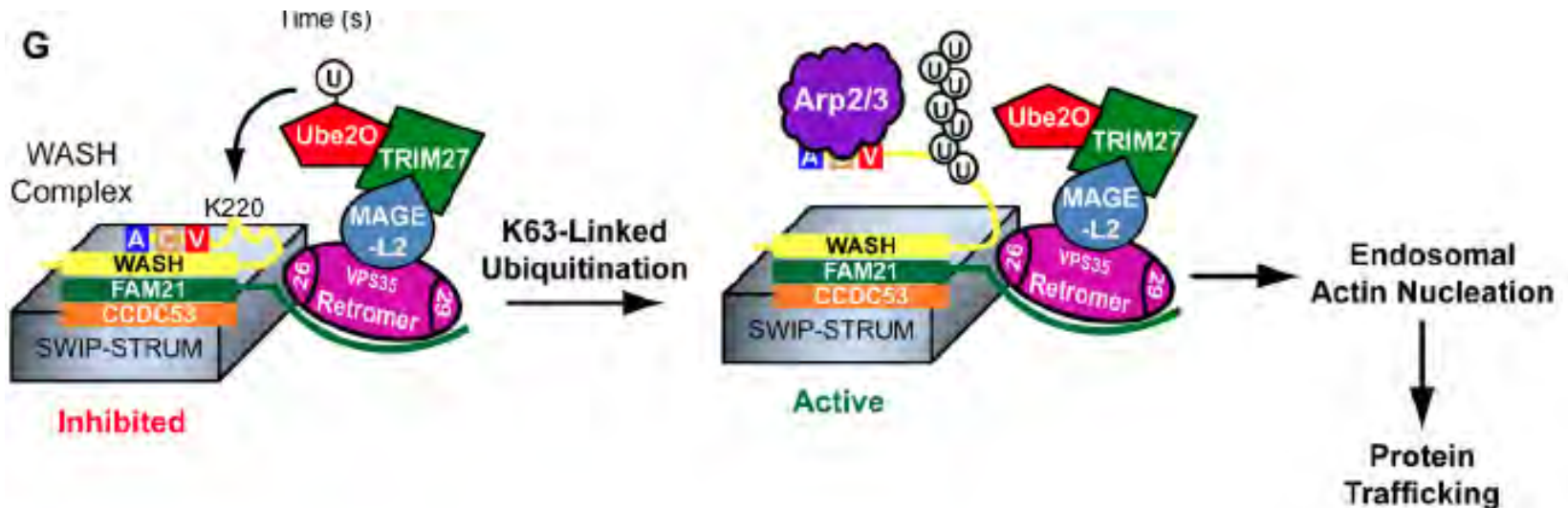
Approach: [Five FPWR projects underway](#) to investigate various methods to reactivate the maternal, silent gene copy that is still present in children with PWS.



2) Function of PWS genes

What do PWS genes normally do in the brain?

Approach: Four FPWR projects and one contracted program underway to study the role of MAGEL2 in autism, oxytocin function, leptin responses. A MAGEL2-deficient rat is being developed for improved pharmacologic and behaviour testing.



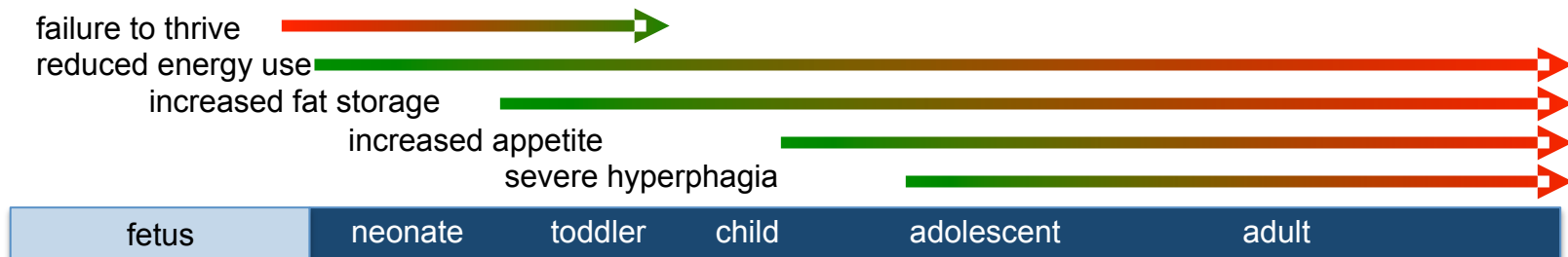
Posters from the Wevrick Laboratory

- **Herman Cortes:** MAGEL2 in autism networks
Funded by PWSA-Alberta and the Simons Foundation
- **Igor Pravdivyi:** MAGEL2 in the transition to hyperphagia
Funded by FPWR
- **Chloe Luck:** MAGEL2 in reward-based eating
- **Dila Kamaludin:** MAGEL2 in the hypothalamus and in muscle
- **Vanessa Carias:** MAGEL2 in protein degradation
- **Methsala Wijesuriya:** MAGEL2 in leptin receptor function

3) *Appetite and obesity*

Why do children switch from apparently having little appetite and 'failure to thrive' to having an overwhelming drive to eat in late childhood/adulthood?

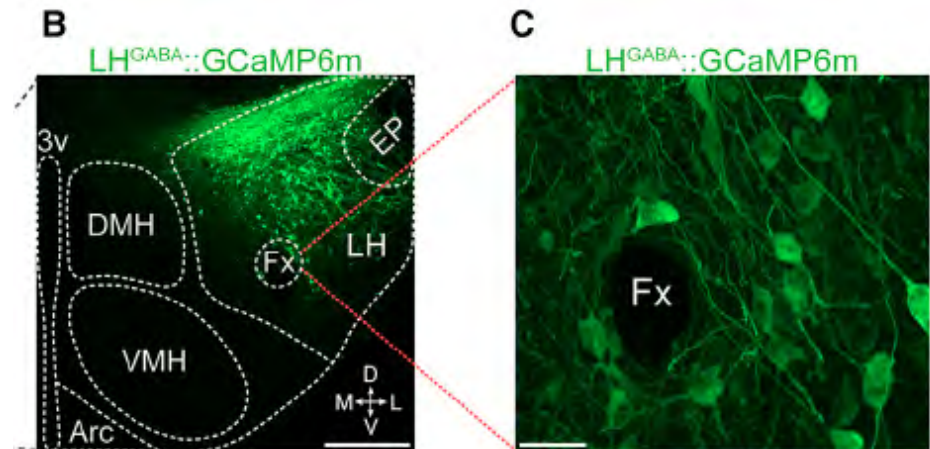
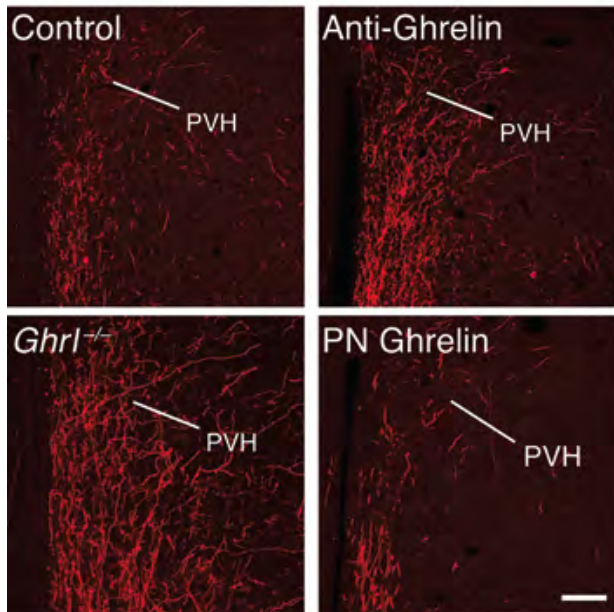
Approach: [Six funded projects and three clinical trials](#) underway to understand why the weight gain starts and how to correct excessive hunger



Understanding Neural Circuits

Stuber and colleagues: Visualizing hypothalamic network dynamics for appetitive and consummatory behaviors. Cell 2015

Used advanced technologies to delineate neural networks controlling food intake in normal mice; currently applying technique to PWS mice.



Bouret and colleagues. Neonatal ghrelin programs development of hypothalamic feeding circuits. J Clin Invest. 2015.

Examined the consequences of high levels of ghrelin on feeding circuits in the brain.

The Foundation for Prader-Willi Research - First Scientific Conference
Date: September 25th, 2015

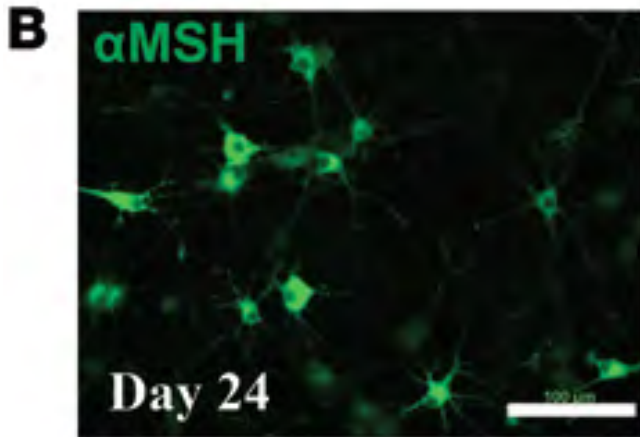
“Neurobiology of PWS”

before the
Annual FPWR Conference September 25-27, 2015

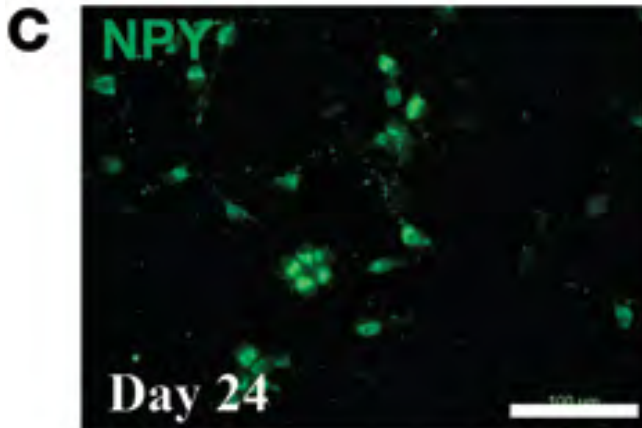


Using iPS cells to model hypothalamic changes

Rudy Leibel and colleagues: Differentiation of hypothalamic-like neurons from human pluripotent stem cells. J Clin Invest. 2015



First demonstration that iPS cells can differentiate into hypothalamic neurons in vitro – this will allow study of appetite-controlling neurons from individuals with PWS.

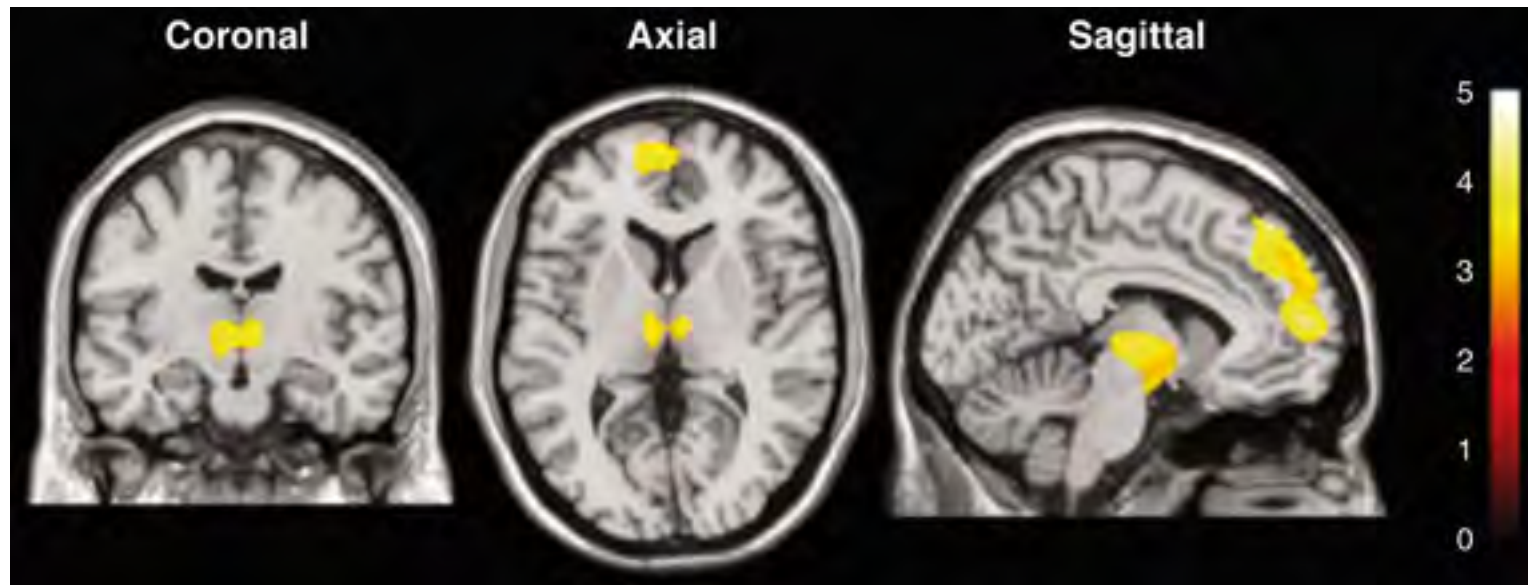


Opens new avenues for the identification of novel targets for therapy

4) *Mental health*

How can we understand more about the neurobiology of mental illness, identify early markers, and reduce family stress?

Approach: [Seven funded projects and the FPWR Mental Health Workshop.](#)



PWS Mental Health Research Strategy Workshop

Bethesda, MD March 1-3, 2015

Two day workshop brought together ~45 international experts in mental health to prioritize research questions

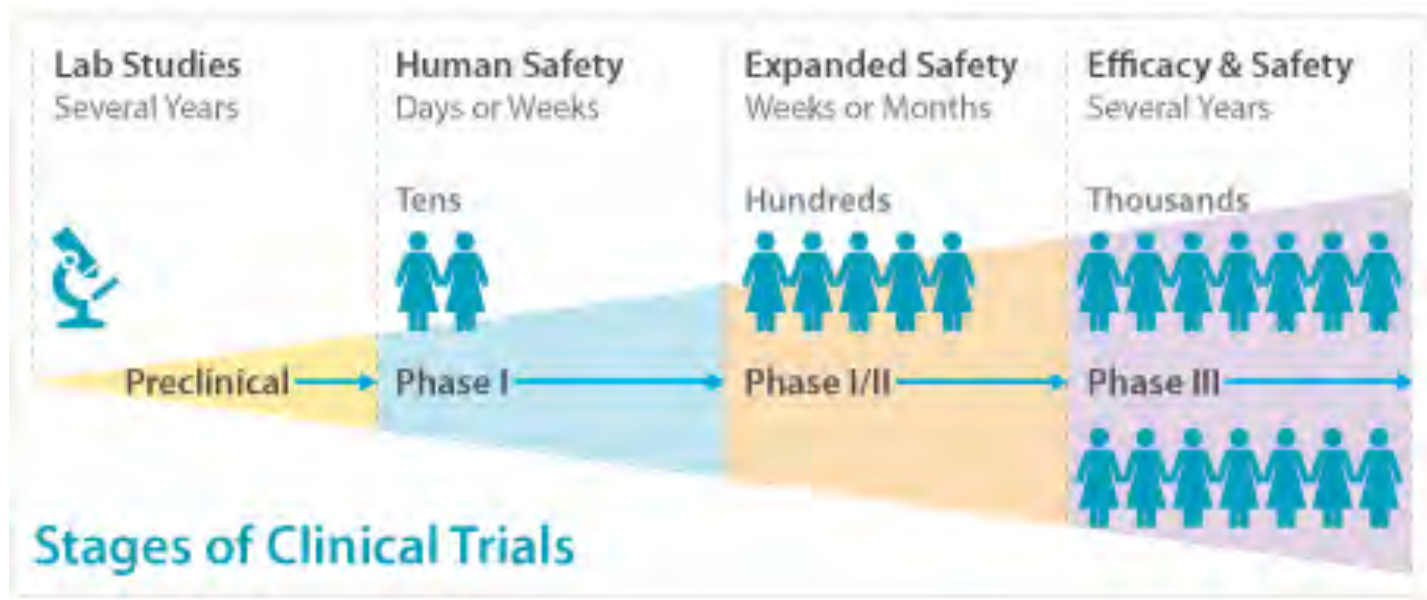
Key questions and recommendations

- Fully apply a range of technologies and model systems to understand the underpinnings of behavior and mental illness in PWS.
- Better characterize the prodromal phase of psychosis in PWS to identify those at highest risk. Develop a prevention trial.
- Adapt state of the art behavioral interventions to PWS, evaluate efficacy.
- Develop appropriate endpoints for assessing the efficacy of behavioral and pharmacological interventions.

5) PWS Therapeutics

Can drugs in development or in use be beneficial in PWS?

- [FPWR PWS Therapeutics Group](#)
- [Global PWS Registry](#)
- [PWS Clinical Trials Program](#)



6) *Facilitate new research*

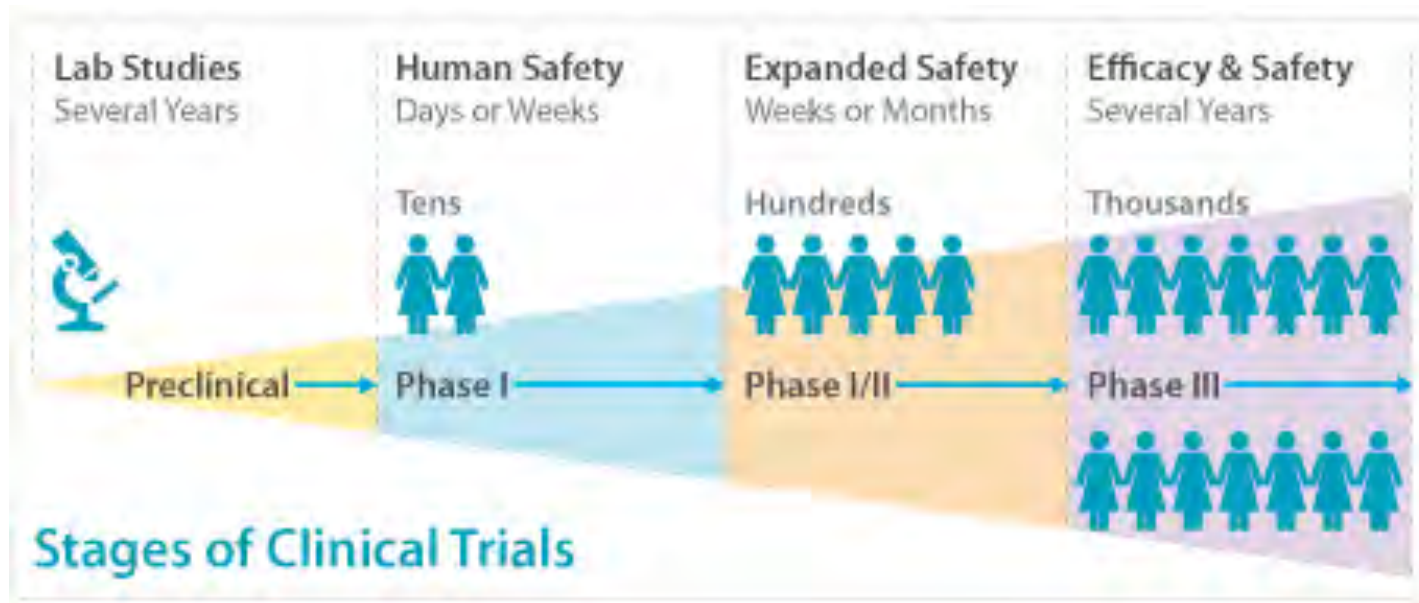
What are the underlying mechanism by which disruption of PWS genes leads to the characteristics of PWS?

- Fund basic science research projects to feed the pipeline
- Develop long-term resources
- Invite new and non-PWS researchers to participate in grant reviews, conferences, and pilot studies.

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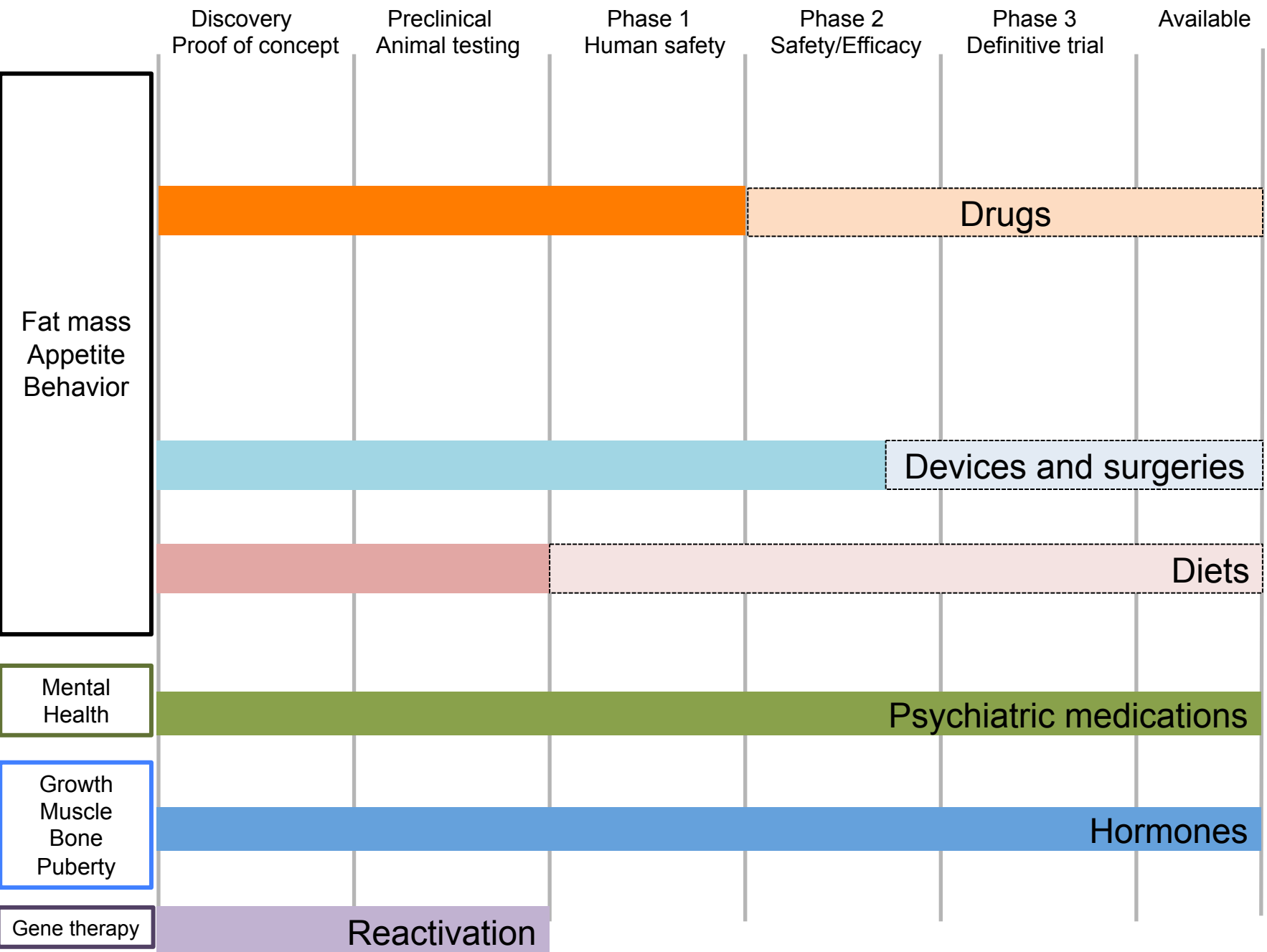




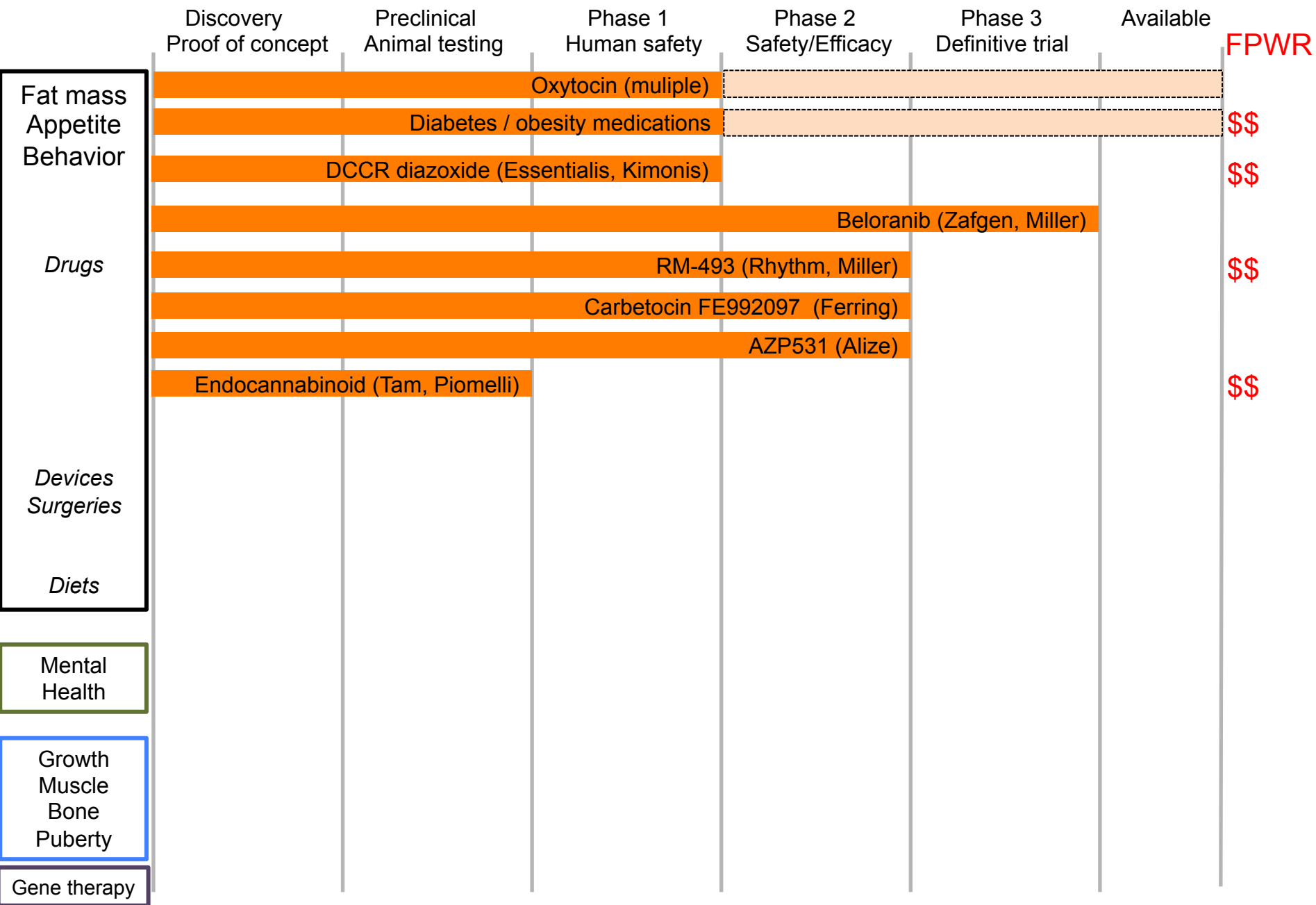
GLOBAL PRADER-WILLI SYNDROME REGISTRY



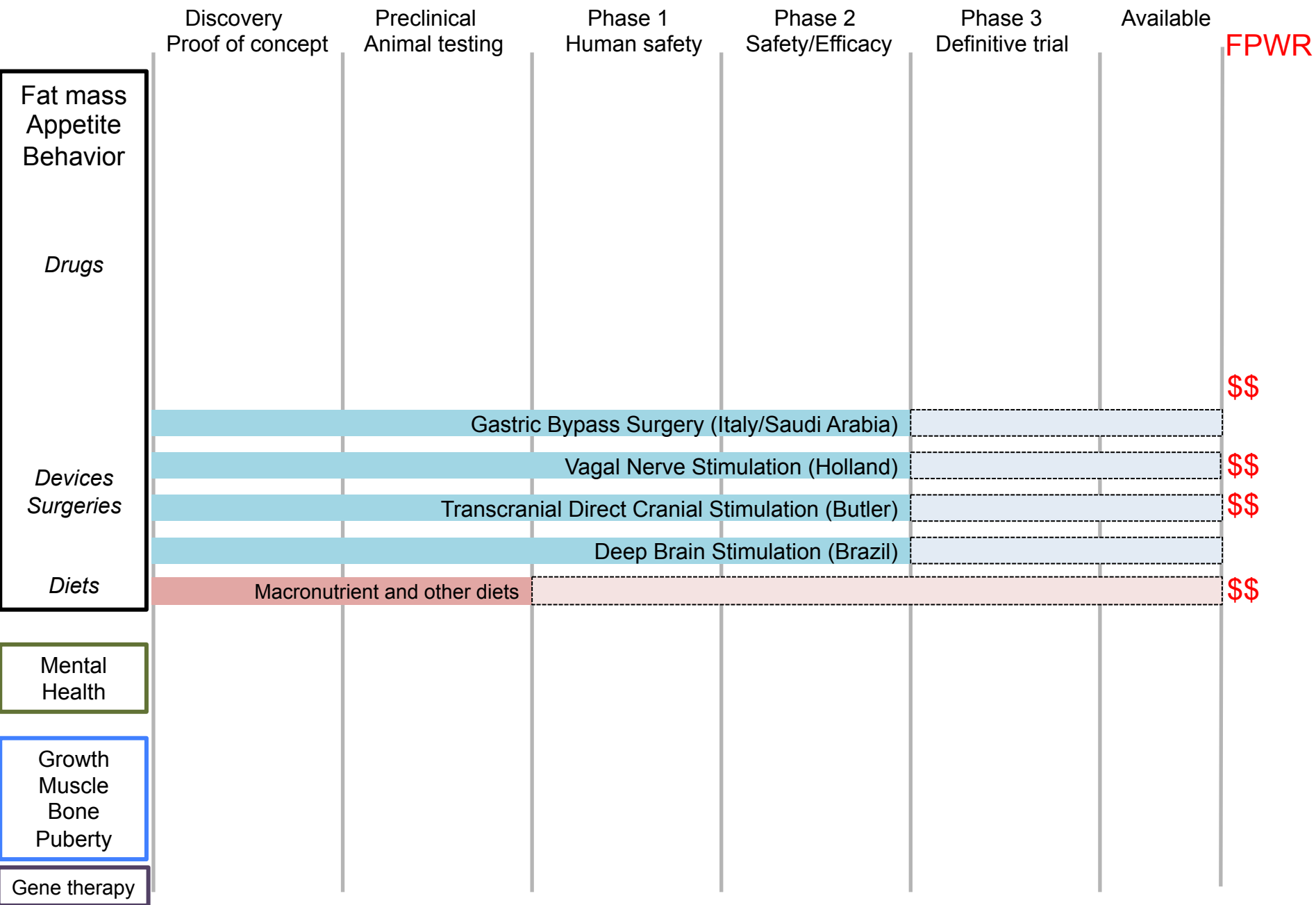
Prader-Willi Syndrome Therapeutics Pipeline



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Prader-Willi Syndrome Therapeutics Pipeline

Discovery
Proof of concept

Preclinical
Animal testing

Phase 1
Human safety

Phase 2
Safety/Efficacy

Phase 3
Definitive trial

Available

FPWR

Fat mass
Appetite
Behavior

Drugs

Devices
Surgeries

Diets

Psychiatric medications

Mental
Health

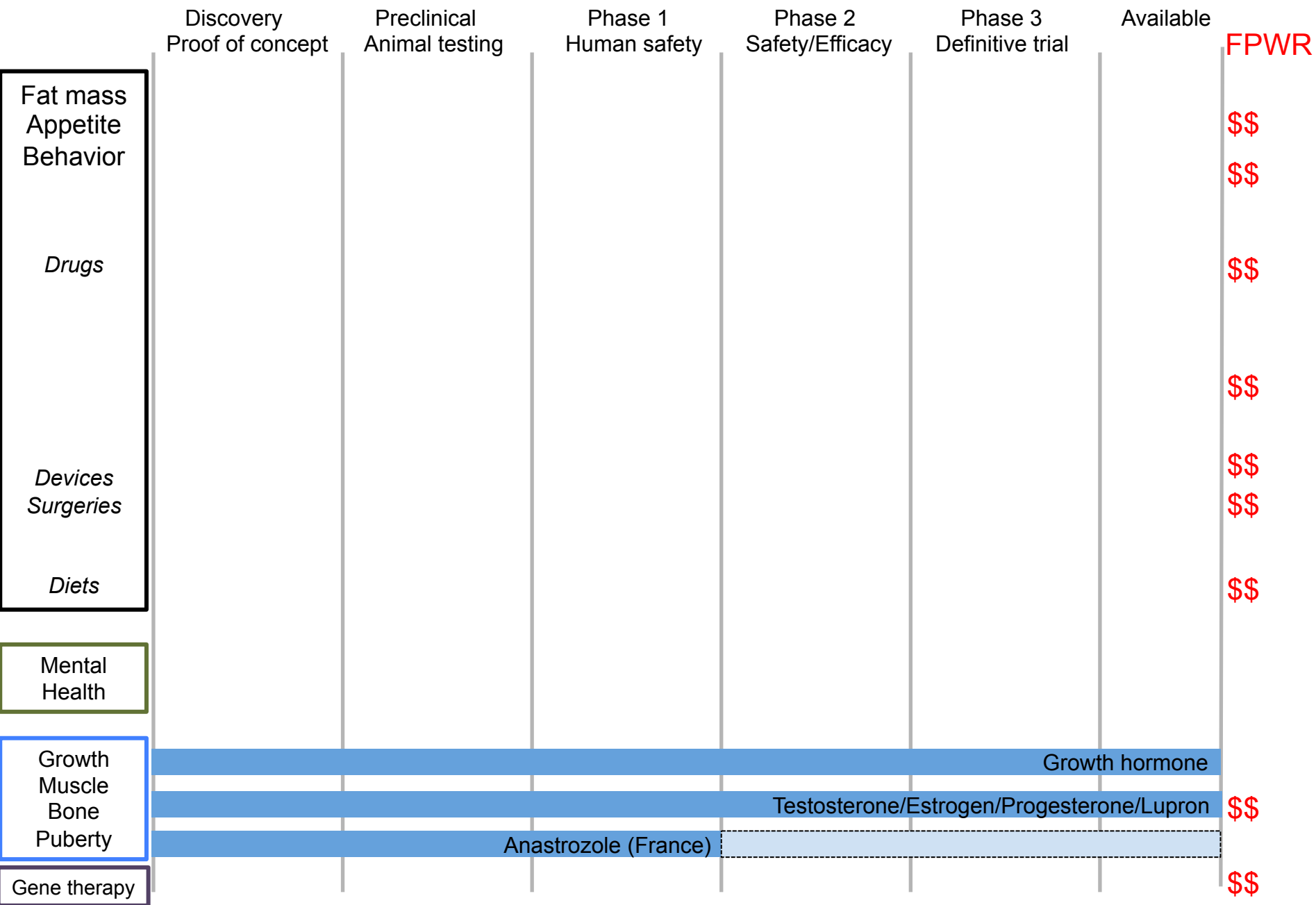
Modafinil

N-acetylcysteine

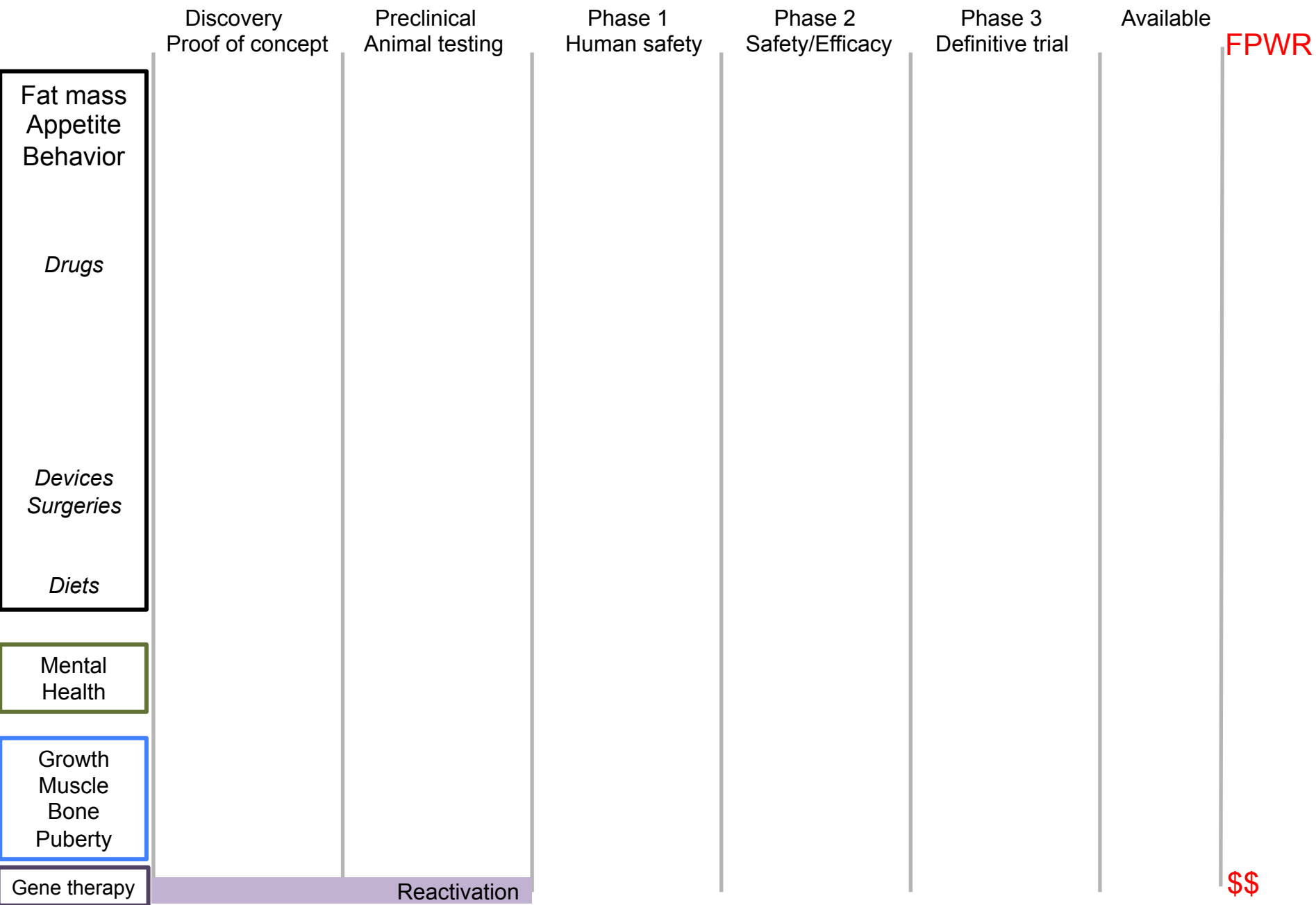
Growth
Muscle
Bone
Puberty

Gene therapy

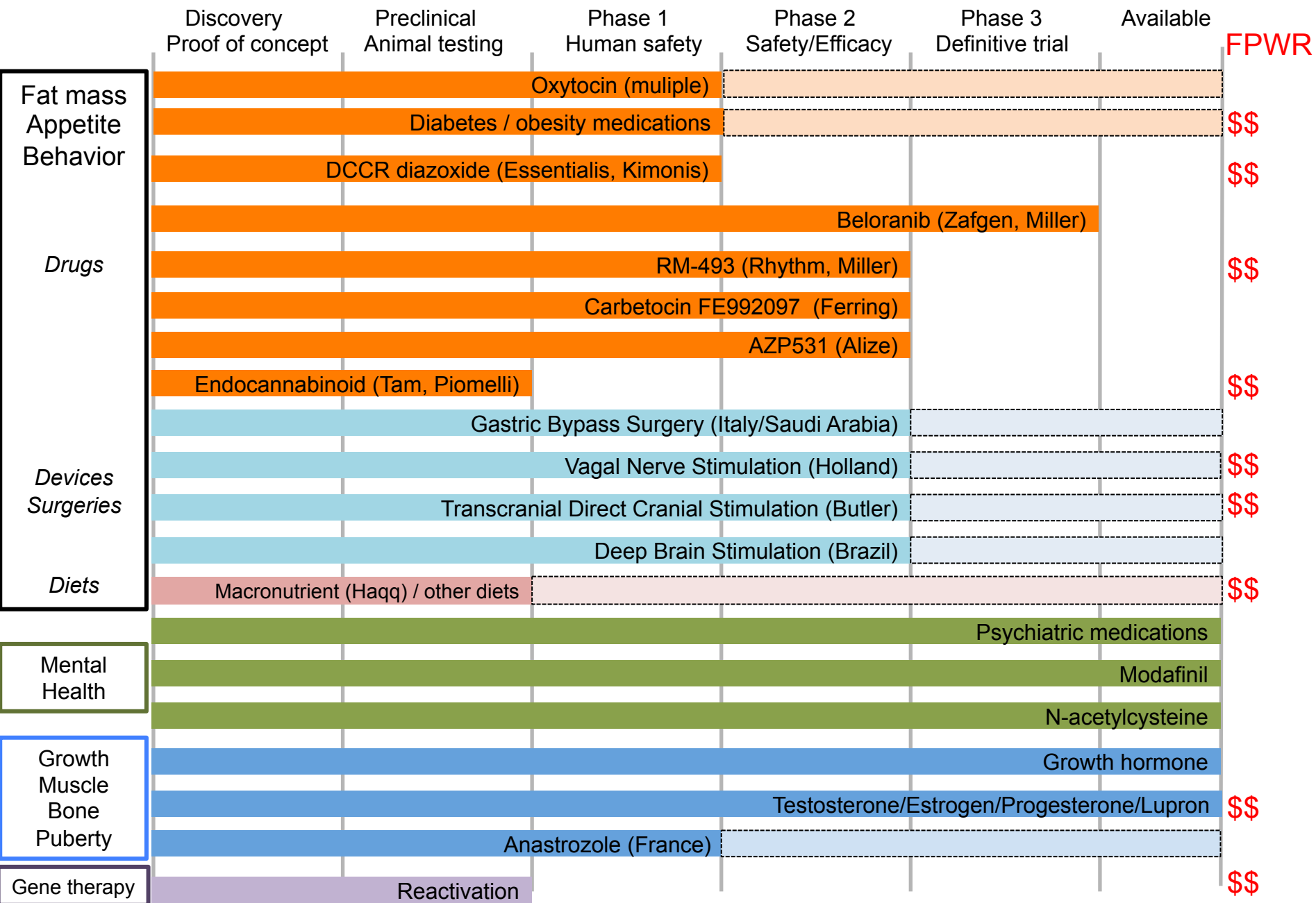
Prader-Willi Syndrome Therapeutics Pipeline



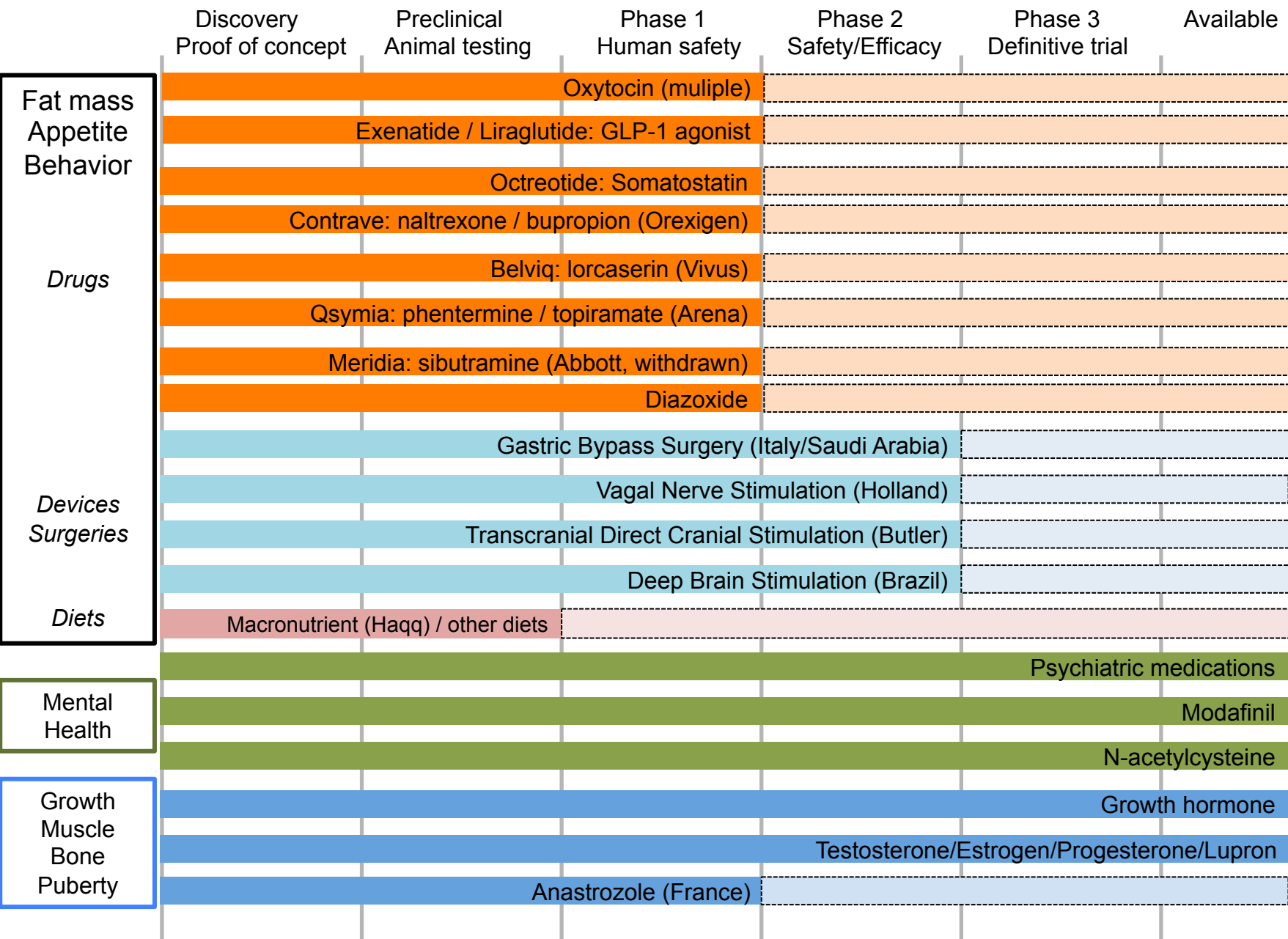
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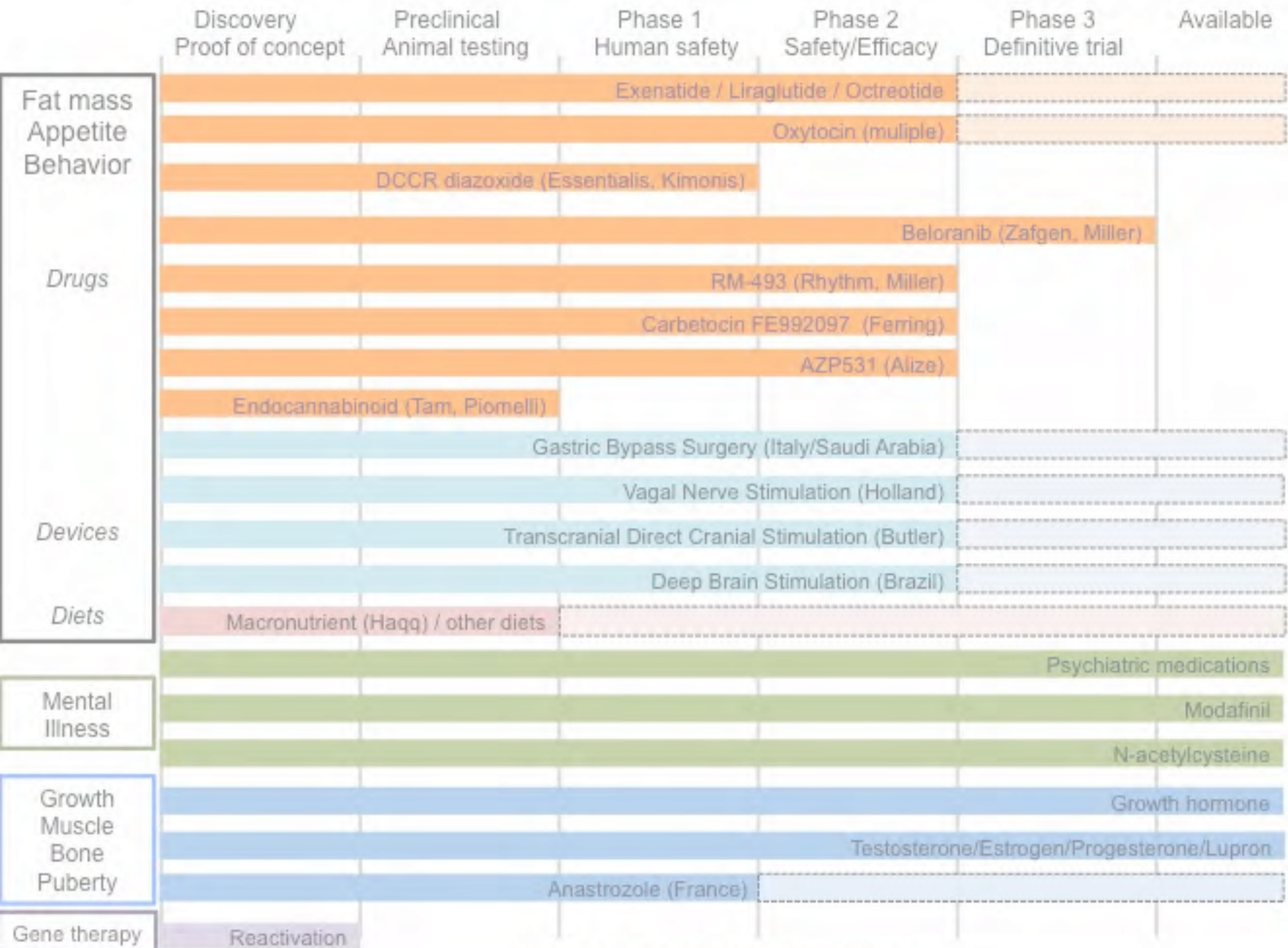
Therapeutics previously approved but not specifically tested in PWS



Prader-Willi Syndrome Novel Therapeutics

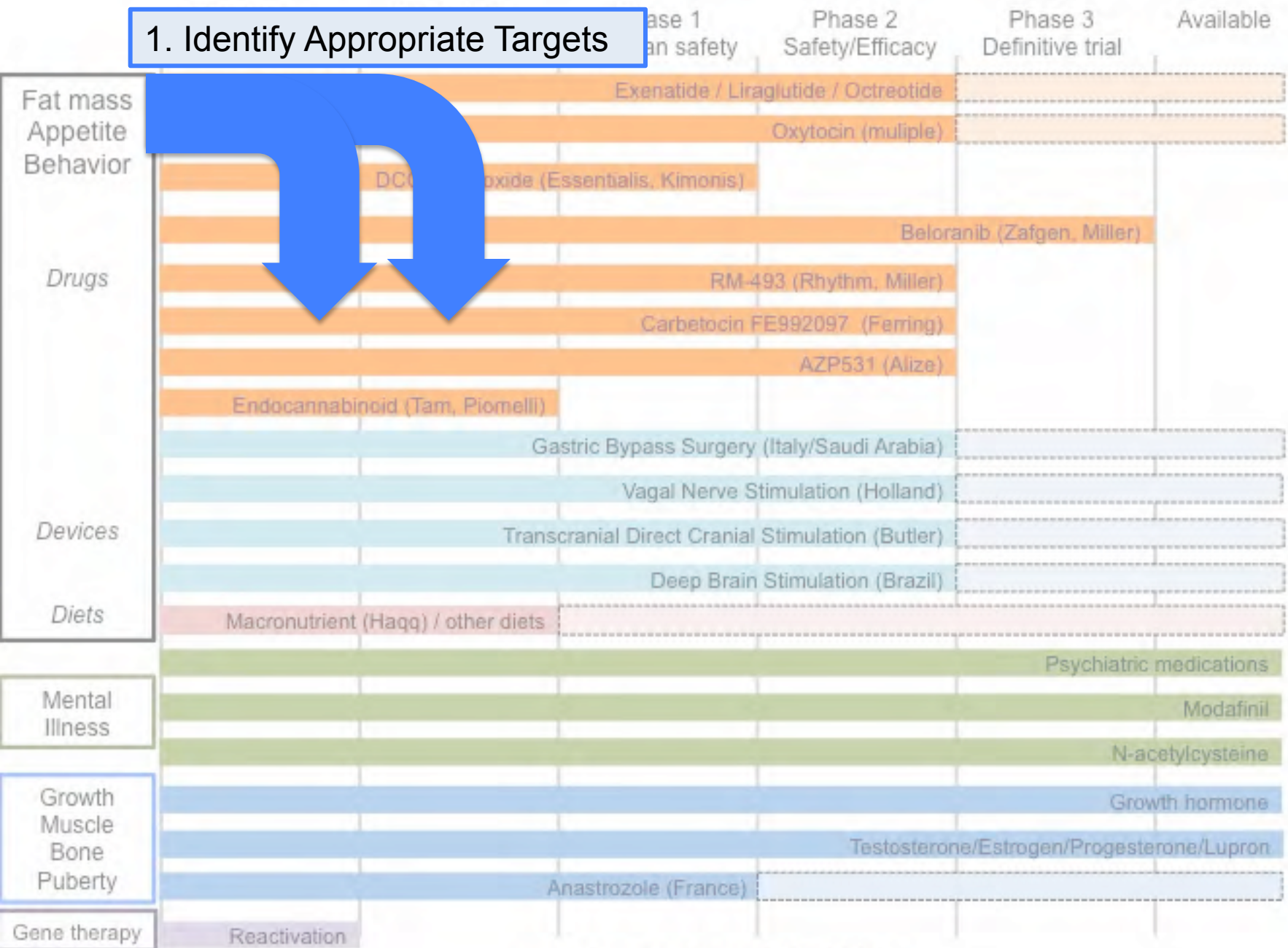


FEED the PWS Pipeline



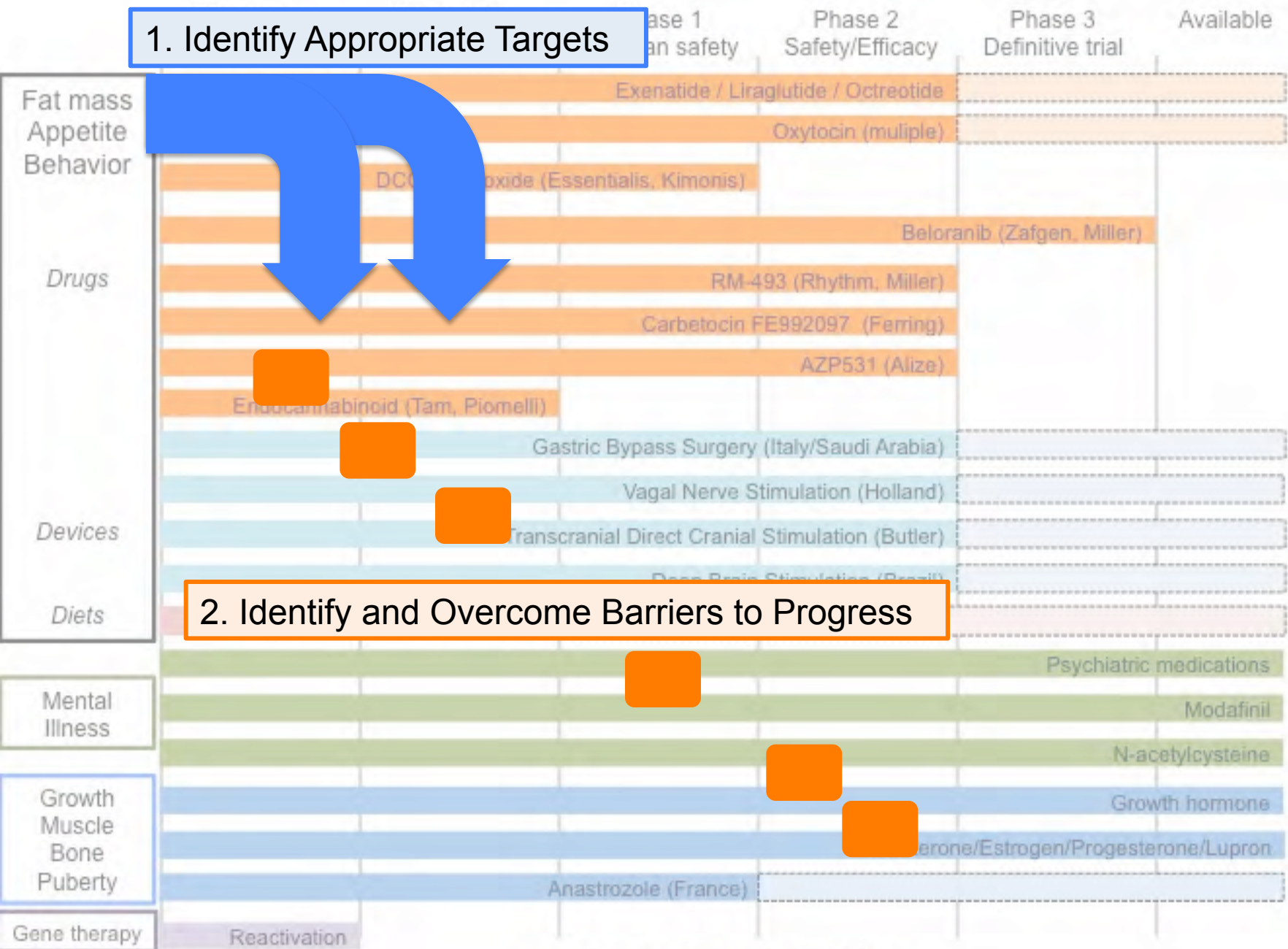
FEED the PWS Pipeline

1. Identify Appropriate Targets



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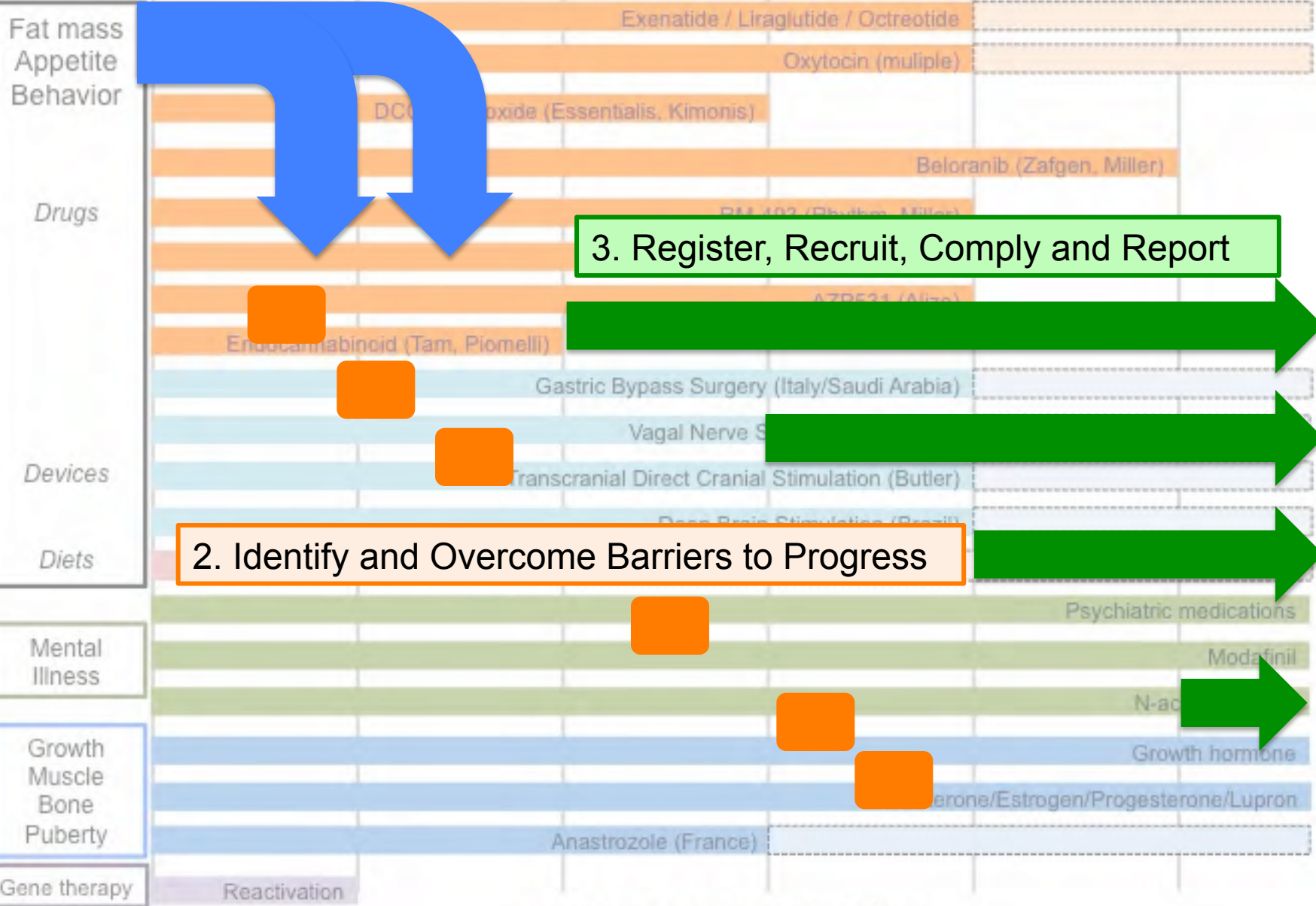


2. Identify and Overcome Barriers to Progress

FEED the PWS Pipeline

1. Identify Appropriate Targets

Phase 1
Phase 2
Phase 3
Available



3. Register, Recruit, Comply and Report

2. Identify and Overcome Barriers to Progress

Identify and overcome barriers to progress

- Feed the research pipeline
- Enlist experts from other medical and research fields
- Facilitate clinical trials

Investments and Opportunities

Continued investment in:

1. Centers of Excellence, Program Research, Investigator initiated research, and Research Tools
2. Workshops, Research Days, and Working Groups
3. Communication with parents and clinicians for involvement in FPWR and for recruitment into clinical studies and trials
4. Management of the PWS Clinical Trials Program at FPWR

What can you do???

What can you do???

- ✓ Tell anyone who will listen about PWS!
- ✓ Commit to eliminating the challenges of Prader-Willi syndrome through the advancement of research!
- ✓ Come to a conference!
- ✓ Take One Small Step!
- ✓ Join the Global PWS Registry!
- ✓ Consider enrolling in a clinical study!
- ✓ Become an advocate reviewer!

