REZOLUTE

All about RZ358: A Novel, New Potential Therapy for Congenital HI

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Forward Looking Statements

Statements in this presentation that are not descriptions of historical facts are forward-looking statements relating to future events, and as such all forward-looking statements are made pursuant to the Securities Litigation Reform Act of 1995. Statements may contain certain forward-looking statements pertaining to future anticipated or projected plans, performance and developments, as well as other statements relating to future operations and results. Any statements in this presentation that are not statements of historical fact may be considered to be forward-looking statements. Words such as "may," "will," "expect," "believe," "anticipate," "estimate," "intends," "goal," "objective," "seek," "attempt," or variations of these or similar words, identify forward-looking statements.

These forward-looking statements by their nature are estimates of future results only and involve substantial risks and uncertainties, including but not limited to risks associated with the uncertainty of clinical trial results, future financial results, additional financing requirements, development of new products, the impact of competitive products or pricing, technological changes, the effect of economic conditions and other uncertainties detailed from time to time in our reports filed with the Securities and Exchange Commission.

Our actual results may differ materially from expectations based on the above factors and other factors more fully described in our public filings with the U.S. Securities and Exchange Commission, which can be reviewed at www.sec.gov.

Presentation Objectives

- Monoclonal antibody background
- How RZ358 works
- Phase 2b (RIZE) study results
- Next steps

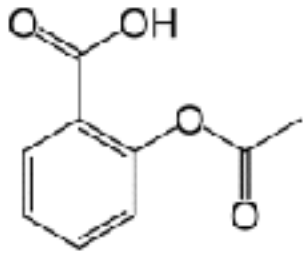
Monoclonal Antibody Background

Jeff

What is Medicine and How Are Proteins Used As Medicine?

- **Medicine -** a substance or preparation used in treating disease
  - *Stop something from happening, or replace something that isn't working*

- **Two common types of medicine:**
  - **Small molecules** (~2,700 FDA approved)
    - Aspirin (Headache)
    - Prilosec (Antacid/Heartburn)
    - Diazoxide (HI)



  - **Proteins** (~380 FDA approved)
    - Insulin (Diabetes)
    - Clotting Factor VIIa (Hemophilia)
    - Antibodies (Cancer, Psoriasis, Asthma)
      - Four different types of antibodies (IgG1, IgG2, IgG3 and IgG4)

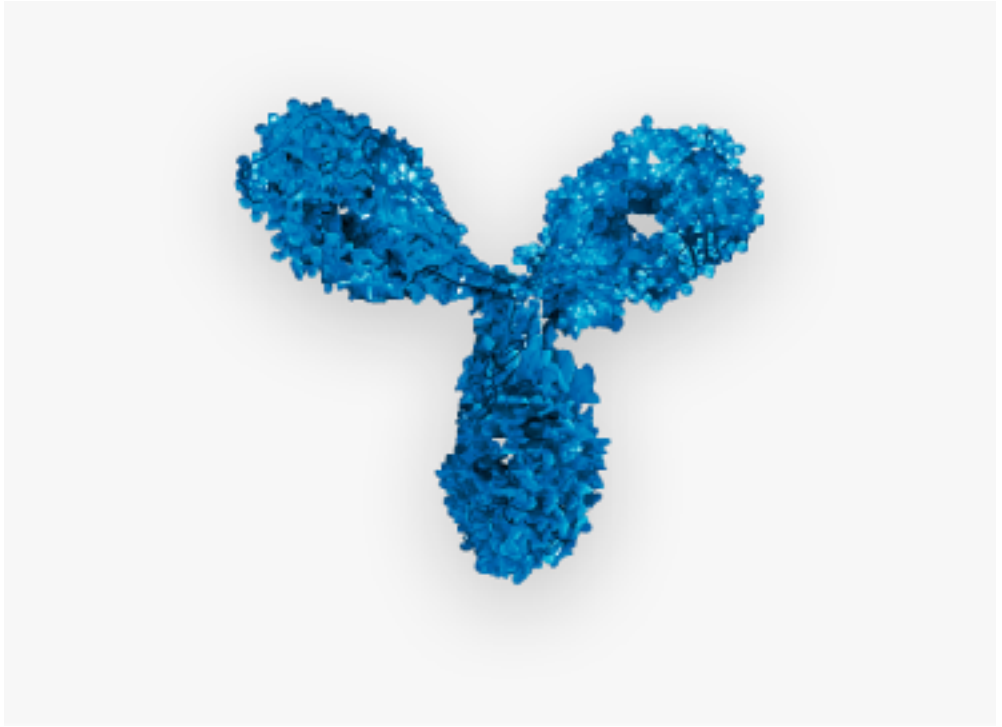
https://www.nature.com/articles/s41392-021-00572-w

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6988726/pdf/nihms-1065954.pdf

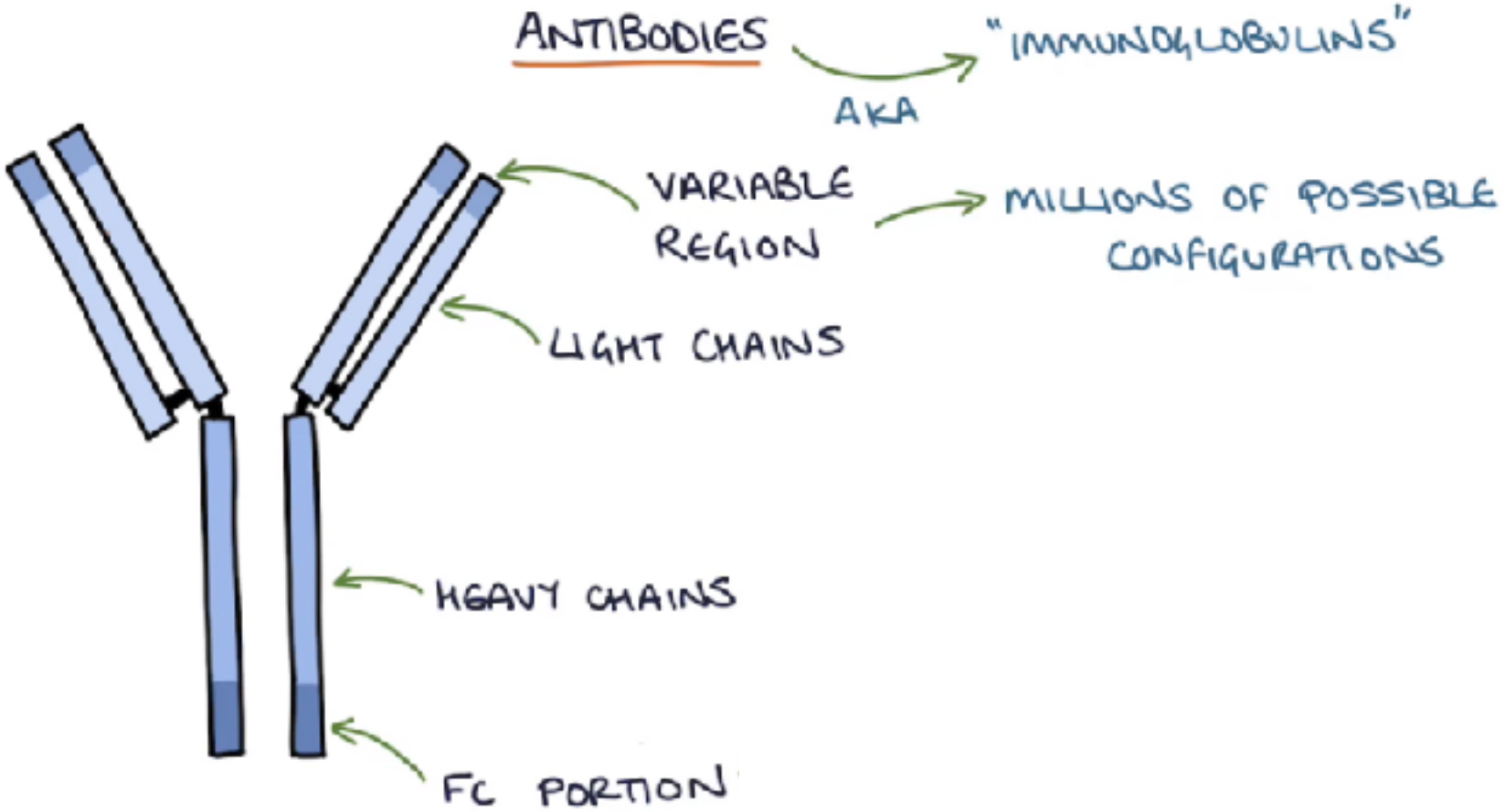
https://www.merriam-webster.com/dictionary/medicine

Antibodies are Diverse and Customizable Protein Therapies

- An antibody is a “Y-shaped” protein used that can be designed to tightly and specifically bind to other proteins
  - The “Y” arm is where the antibody binds to a protein
- Antibodies can be produced by your own immune system (such as in response to illness, like COVID) *or…*
- Antibodies can be designed by scientists and manufactured to bind to and change the function of specific parts of your body
  - Like the insulin receptor
- Manufactured antibodies can be used as medicine

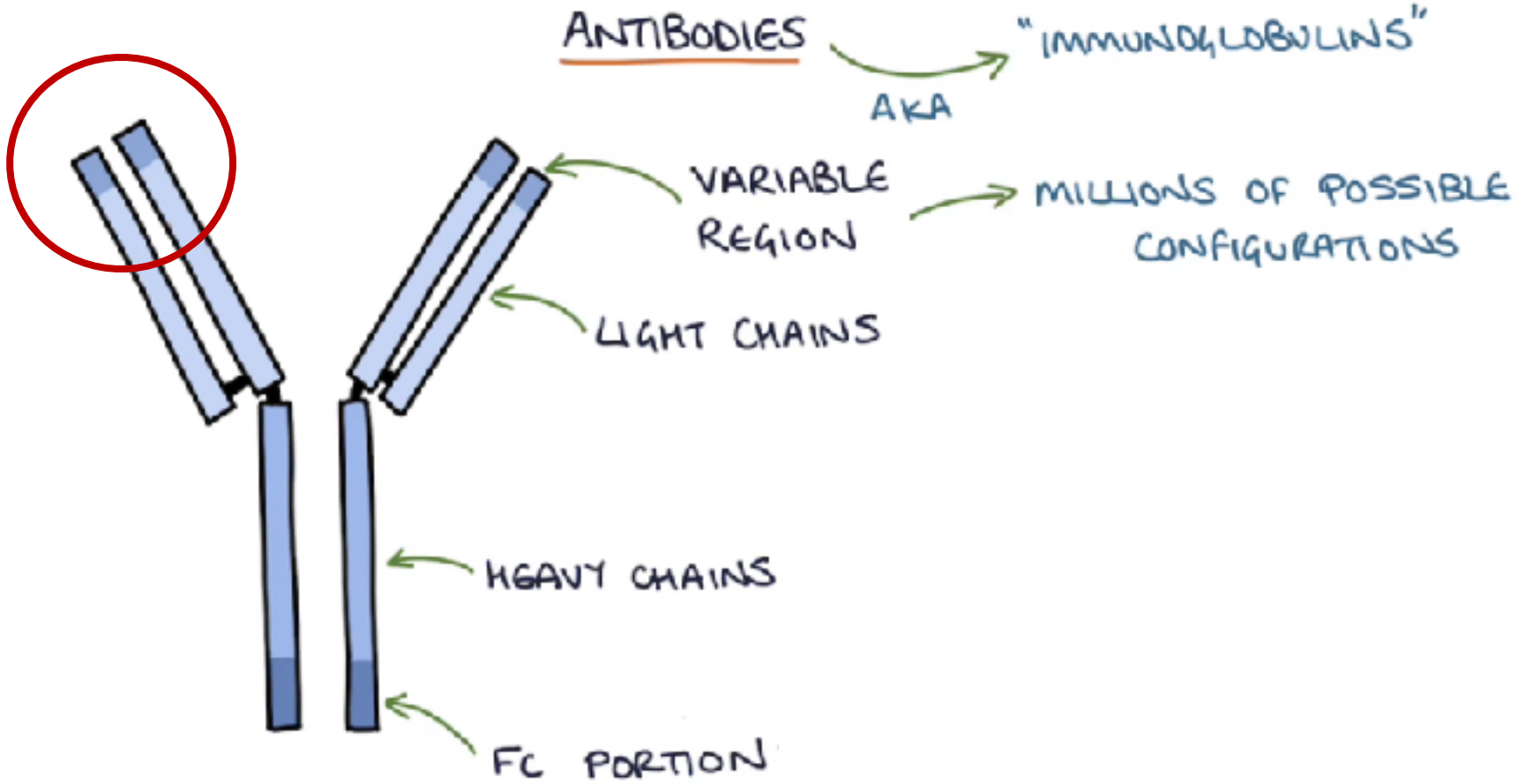


The Different Parts of an Antibody Lead to Different Functions



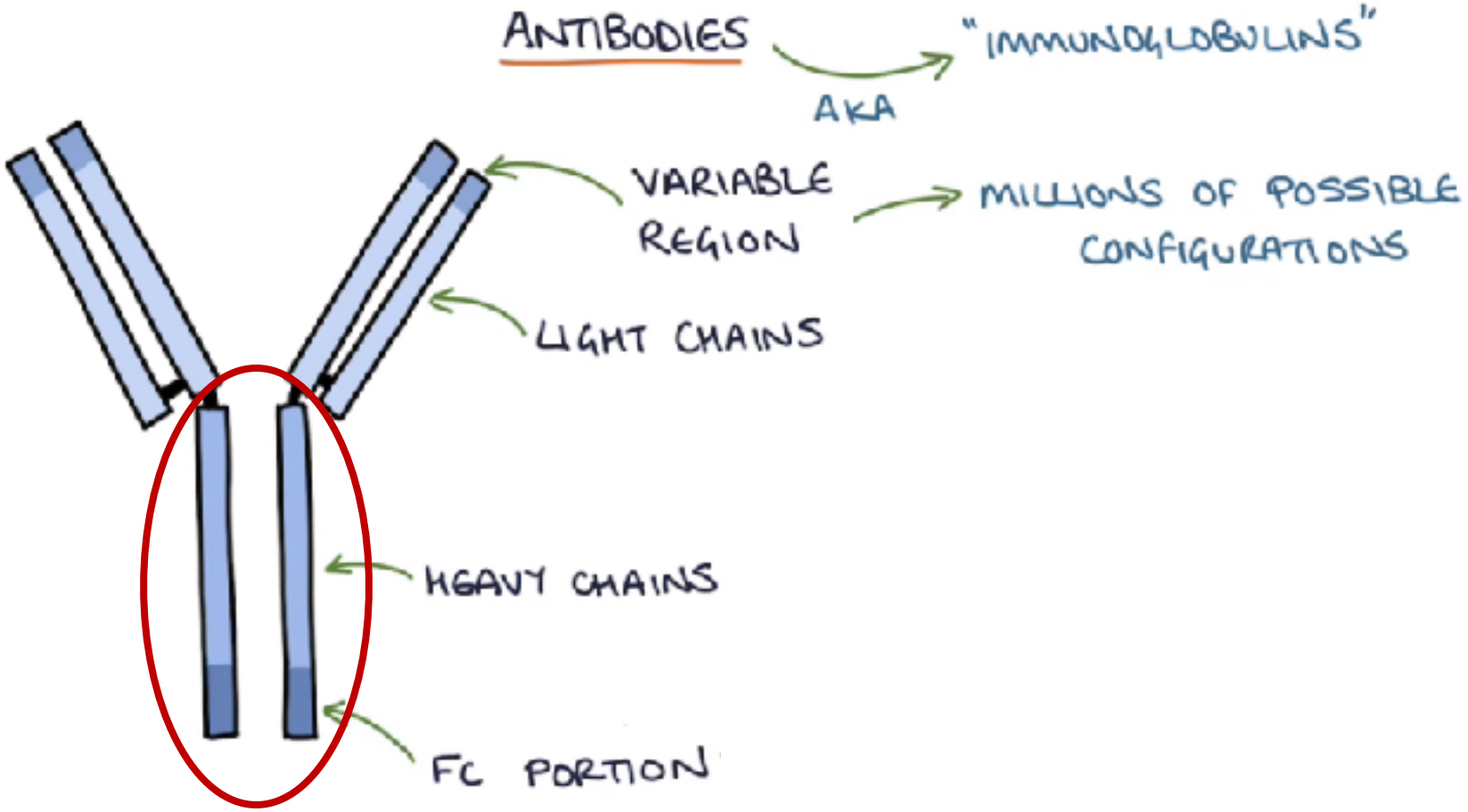
The Different Parts of an Antibody Lead to Different Functions

- The **Variable Region** tightly binds to specific parts of target proteins
- The **Variable Region** of the antibody can be customized for any protein of interest



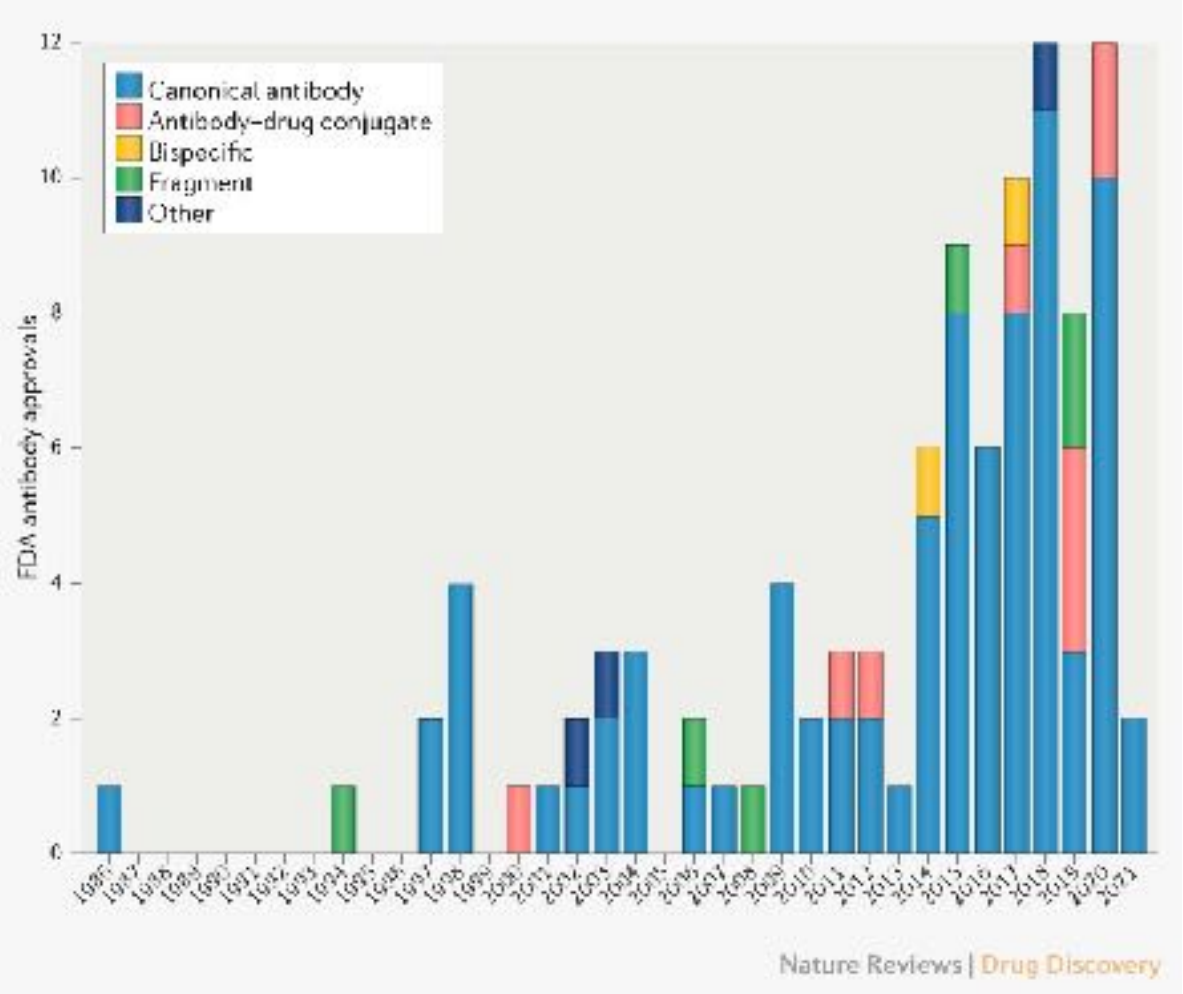
The Different Parts of an Antibody Lead to Different Functions

- The **Variable Region** tightly binds to specific parts of target proteins
- The **Variable Region** of the antibody can be customized for any protein of interest
- The **Heavy Chains** of an antibody increase the amount of time the antibody stays in your body (dosing every 2-4 weeks) and may be involved in immune signaling



Antibodies are a Precedented and Promising Therapeutic Technology

- Over 100 different antibody therapies have been approved by the FDA
- The FDA approved the first therapeutic antibody in 1986
- Antibody approvals are increasing over time
- Antibodies are often more specific and more potent than small molecule therapeutics
- Off-target/non-specific effects of antibodies are often less than with small molecules



https://www.nature.com/articles/d41573-021-00079-7
https://www.uptodate.com/contents/overview-of-therapeutic-monoclonal-antibodies

How RZ358 Works

Jeff

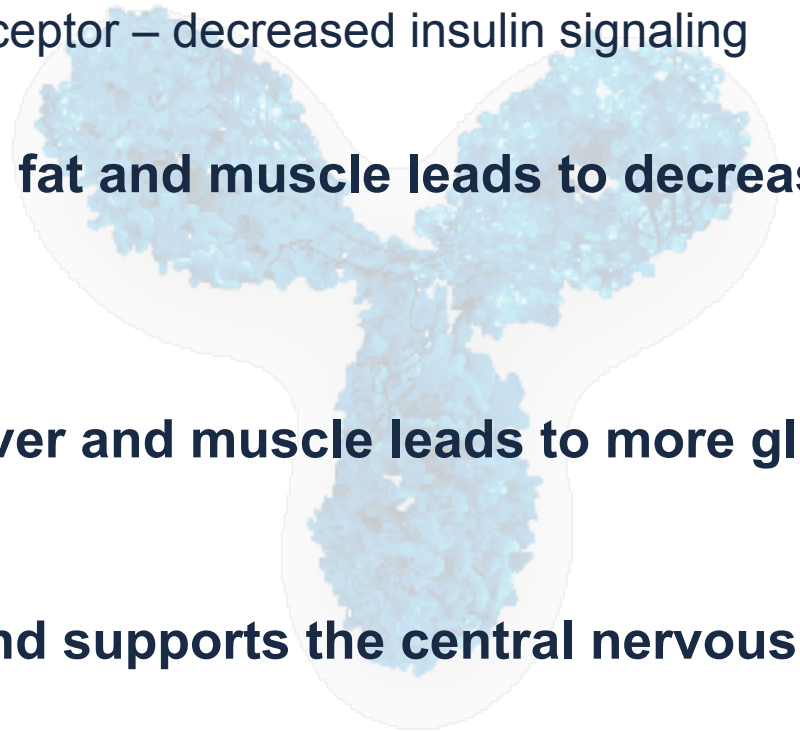
RZ358 is an Antibody That Specifically Binds to the Insulin Receptor and Changes How the Body Responds to Insulin

1. **RZ358 binds to *the side of* the insulin receptor and decreases insulin signaling in cells**
   - Doesn't compete with insulin at the insulin binding site of the insulin receptor
   - RZ358 decreases how tightly insulin binds to the insulin receptor – decreased insulin signaling

2. **Decreased insulin signaling in tissues like the liver, fat and muscle leads to decreased glucose transporters on the surface of these cells**
   - Insulin regulates glucose transporter density on cells

3. **Fewer glucose transporters on the surface of fat, liver and muscle leads to more glucose remaining in the bloodstream**

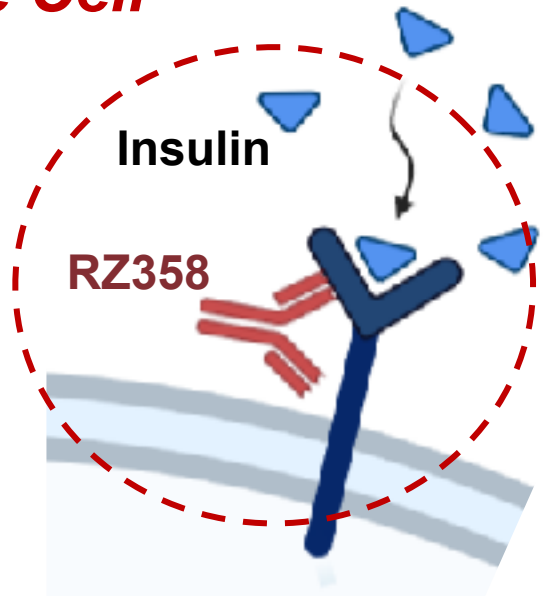
4. **More glucose is therefore left in the bloodstream and supports the central nervous system (your brain)**



RZ358 Disrupts Insulin Signaling at the Insulin Receptor and Slows Glucose Uptake into Cells

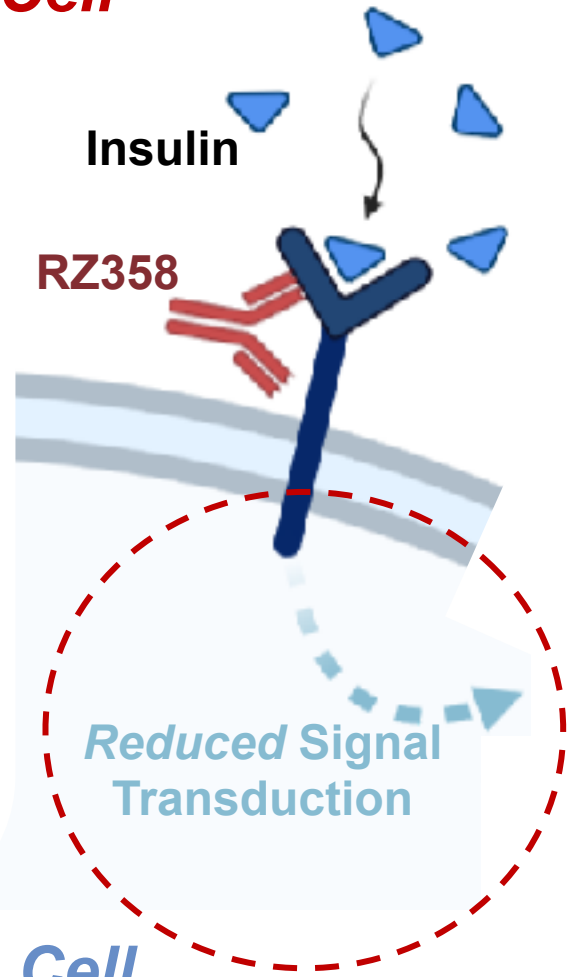
Outside the Cell

- RZ358 binds to the side of the Insulin Receptor
- This decreases how tightly Insulin binds to its receptor



RZ358 Disrupts Insulin Signaling at the Insulin Receptor and Slows Glucose Uptake into Cells

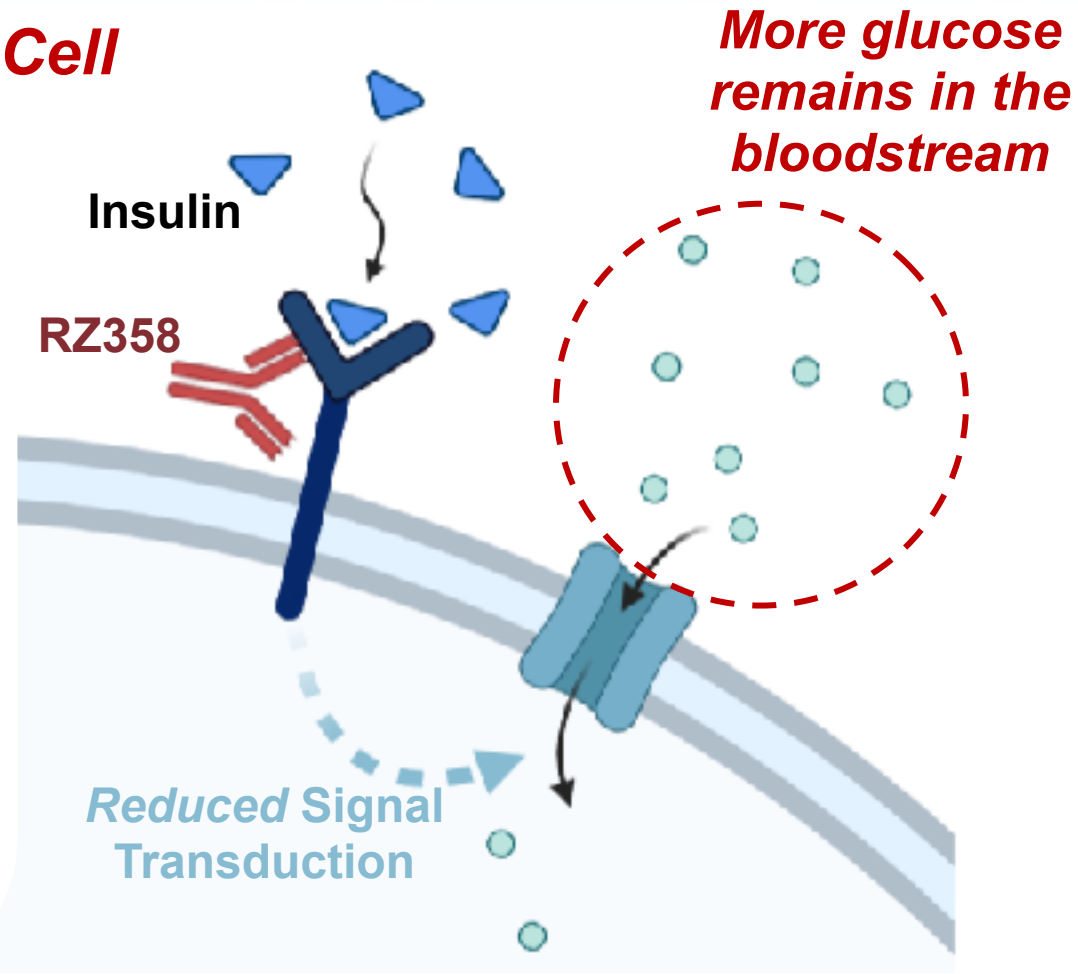
- **RZ358 decreases insulin induced signaling that occurs inside the cell**



RZ358 Disrupts Insulin Signaling at the Insulin Receptor and Slows Glucose Uptake into Cells

As a result of RZ358 binding…

- Cells take up less glucose leaving more in your bloodstream
- Glucose is the preferred energy source for the central nervous system (brain)



RZ358 Safety Profile – Rationally Designed

IgG2 antibodies have a track record of safety

- The first FDA approved antibody was an IgG2 (1986)
- 16 IgG2's/IgG2-hybrids have been approved by the FDA

Animal studies support an excellent safety profile for RZ358

- Animal proof of concept (POC) and safety studies are performed for all compounds entering clinical trials
- Rodent POC studies highlighted the ability of RZ358 to reduce hypoglycemia induced by hyperinsulinism
  - Reduction of hypoglycemia was dose proportional
- Meaningful hyperglycemia was not observed in primate RZ358 safety studies
- Adequate safety margins were observed in primate studies across the expected human dose range

Phase 2b (RIZE) Study Results

Davelyn

RIZE Study Summary

- Study was conducted primarily in a young pediatric population: average ~6.5 years of age
  - Diverse group of patients in the study across gender and genetics
  - Add-on to SOC therapies
    - RIZE again showed that SOC therapies are suboptimal for some CHI patients
    - Patients enrolled had an average of 25% time in a hypoglycemic range at baseline
- RZ358 demonstrated:
  - ~50% improvement in hypoglycemia across all doses and cohorts
  - ~75% improvement in hypoglycemia at the 6 mg/kg and 9 mg/kg cohorts
    - These are the likely two dosing levels to be studied in Phase 3
- RZ358 was generally safe and well-tolerated
- Expected RZ358 concentrations achieved
- Dose and exposure-dependent responses were observed
  - 100% patient response rate with > 50% Hypoglycemia correction at the top dose

Phase 2b Study (RIZE) Overview

Design

Open-label, repeat-dose study in 4 sequential ascending dosing cohorts
(up to 8 patients per cohort)

Population

Congenital HI ≥ 2 years old with continued hypoglycemia on SOC, by specified continuous glucose monitoring (CGM) and self-monitored BG (SMBG) thresholds

Duration

~26 weeks

- Screening – up to 5 weeks
- Treatment – 8 weeks
- Follow Up – 13 weeks

Assessments/ Endpoints

Primary:
Time within range (70-180 mg/dL) by CGM

Secondary: duration/ incidence of hypoglycemia by CGM/SMBG/fasting

Objectives

Repeat-dose safety and pharmacokinetics (PK) in children

Enable registrational Phase 3 planning and preparation for regulatory interactions

Dosing Cohort	Dose Levels and Bi-Weekly Dosing Regimen (mg/kg)			
	Week 1	Week 3	Week 5	Week 7
1	3	3	3	3
2	6	6	6	6
3	9	9	9	9
4	3	6	9	9

Who Participated in the RIZE Study?

Parameter	RZ358 Total (N=23)
Age (Mean, Range)	6.7 (2-22); N=16 ages 2-6
Gender (n, M / F)	13 / 10
Genetics (n, kATP / Other / Unknown)	11 / 3 / 9
CHI Rx (n, %)	20 (87%)
Diazoxide	8 (35%)
SSA (Long-acting/Short-Acting)	7 / 6 (56%)
Other (inc 2+ meds, pancreatectomy, enteral feeding)	9 (39%)
% Time Hypoglycemia (<70 mg/dL) by CGM (Mean, Range, PP Population)	**23** (6-86; n=22)
Hypoglycemia Events / Wk by BGM (Mean, Range, PP Population)	**16** (5-78; n=21)

- Study observations of persistent hypoglycemia on SOC confirm previous study observations
- 16 (70%) had seizure history; 5 (22%) reporting seizures within past 12 months.
- 14 (61%) reported hospitalizations within past year due to CHI-related complications.
- All 23 patients enrolled completed the study.

How Much Improvement in Hypoglycemia Was Seen in the RIZE Study?

Mean (Range)	RZ358 6 mg/kg (n=8)	RZ358 9 mg/kg (n=7) ^
Time in Hypoglycemia (<70 mg/dL) by CGM (%)		
Baseline	22.2	26.5
End of Treatment	9.2	9.4
% Change from BL (p-value)	***-59% (p<0.01)***	***-65% (p=0.07)*** ^
Time in Severe Hypoglycemia (<50 mg/dL) by CGM (%)		
Baseline	5.1	4.3
End of Treatment	1.4	1.7
% Change from BL (p-value)	***-73% (p<0.05)***	***-61% (NS)*** ^
Hypoglycemia Events (<70 mg/dL) by BGM (events/week)		
Baseline	19.2	16.7
End of Treatment	9.9	5.3
% Change from BL (p-value)	***-48% (p=0.1)***	***- 68% (p<0.01)***
Severe Hypoglycemia Events (<50 mg/dL) by BGM (events/week)		
Baseline	5.5	4.2
End of Treatment	1.2	1.1
% Change from BL (p-value)	***-72% (p=0.1)***	***- 74% (p<0.05)***

One patient at 3 mg/kg was excluded from the per protocol BGM analyses for failing to meet pre-specified minimum glucometer testing

^ One patient at 9 mg/kg was excluded from the per protocol CGM and BGM analyses for stopping background therapy while on study; Two 2 year-old patients in 9 mg/kg group wore CGM on the arm which may have impacted their results, but both were used in BGM analysis

Did Most Patients Respond to RZ358 in the RIZE Study?

Responders N (%)	RZ358 3 mg/kg (n=4) #	RZ358 6 mg/kg (n=8)	RZ358 9 mg/kg (n=7) ^	RZ358 Titrate 3-9 mg/kg (n=3)	RZ358 Total (n=22)
≥25% Correction of Hypoglycemia					
Severe (<50 mg/dL)	3 (75%)	7 (88%)	7 (100%)	2 (67%)	19 (86%)
Overall (<70 mg/dL)	3 (75%)	7 (88%)	7 (100%)	3 (100%)	20 (91%)
≥50% Correction of Hypoglycemia					
Severe (<50 mg/dL)	3 (75%)	6 (75%)	7 (100%)	2 (67%)	18 (82%)
Overall (<70 mg/dL)	1 (25%)	7 (88%)	7 (100%)	1 (33%)	16 (73%)
≥75% Correction of Hypoglycemia					
Severe (<50 mg/dL)	1 (25%)	5 (63%)	6 (86%)	2 (67%)	14 (64%)
Overall (<70 mg/dL)	1 (25%)	3 (38%)	5 (71%)	1 (33%)	10 (45%)

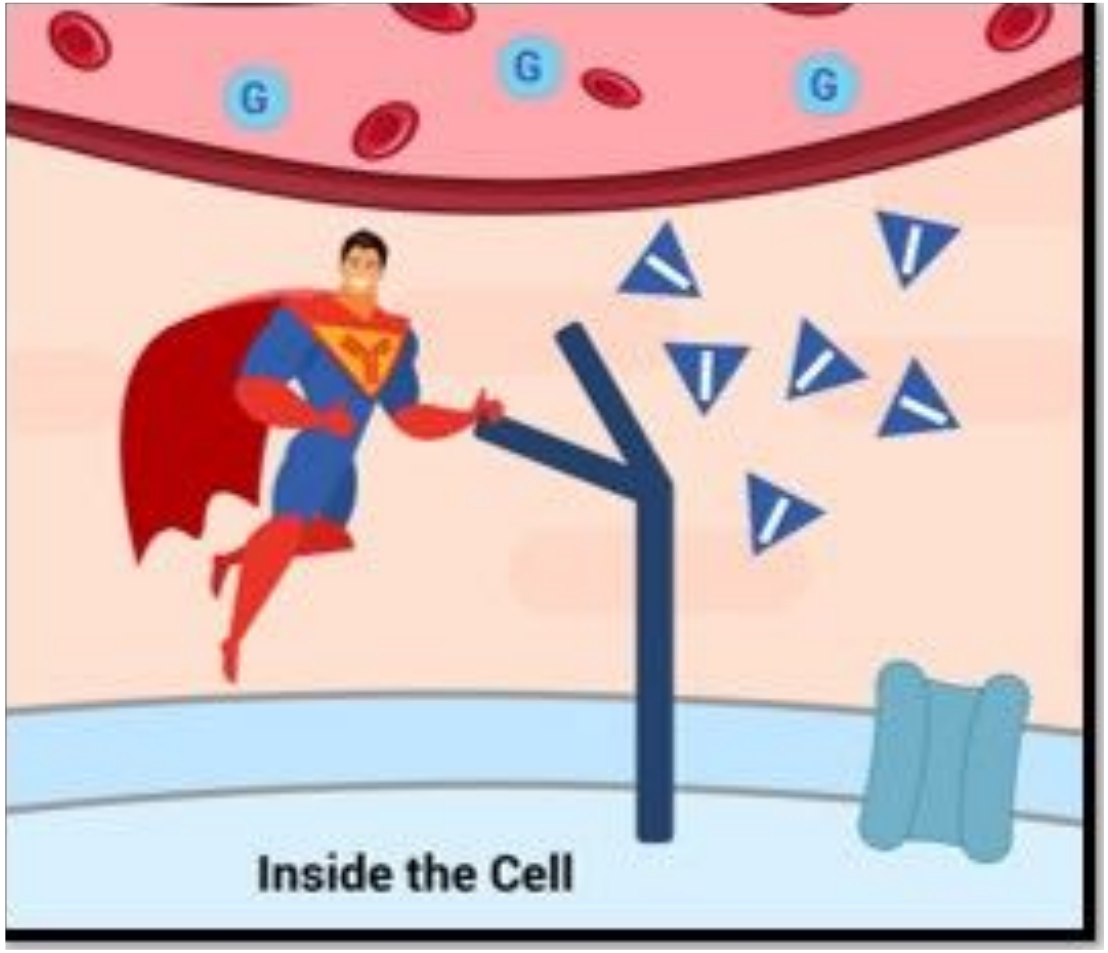
Next Steps

Davelyn

What's next?

- **A very big THANK YOU to:**
  - Study investigators and their teams
  - Patient advocacy groups
  - PATIENTS/FAMILIES enrolled in RIZE!
- **Expanded Access Program**
  - Working to enroll 10 patients in 6 countries
- **Phase 3 Readiness**
  - Regulatory interactions in US, UK & EU
  - Protocol development
  - Study kick-off by end of Q1 2023
- **Patient Listening Sessions**
- **Ongoing subcutaneous formulation activities**
- **Interested potential P3 Investigator? Office hours on Sunday, 1-3pm**

Learn more…



www.rezolutebio.com/for-patients/overview/

Watch our patient-friendly video:

English | French | Spanish | German | Hebrew | Italian