Treatment of Hurler MPSI with a Blood-Brain Barrier Penetrating IgG-Lysosomal Enzyme Fusion Protein

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TRAVERSING THE BBB – PRE-CLINICAL TO CLINICAL TRANSLATION

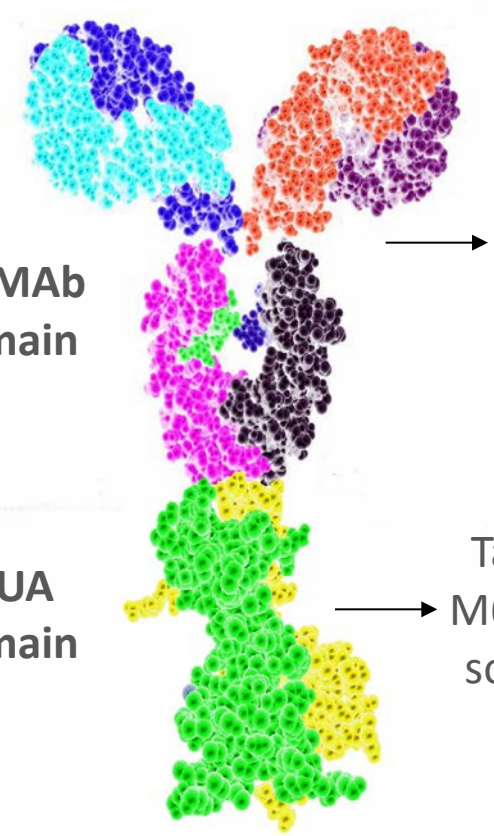
Enabling Novel Treatments for Nervous System Disorders by Improving Methods for Traversing the Blood-Brain Barrier: A Workshop

September 8, 2017, Washington DC

AGT-181: HIRMAb-IDUA fusion protein

A BBB-penetrating form of iduronidase (IDUA)

HIRMAb-IDUA fusion protein



HIRMAb domain

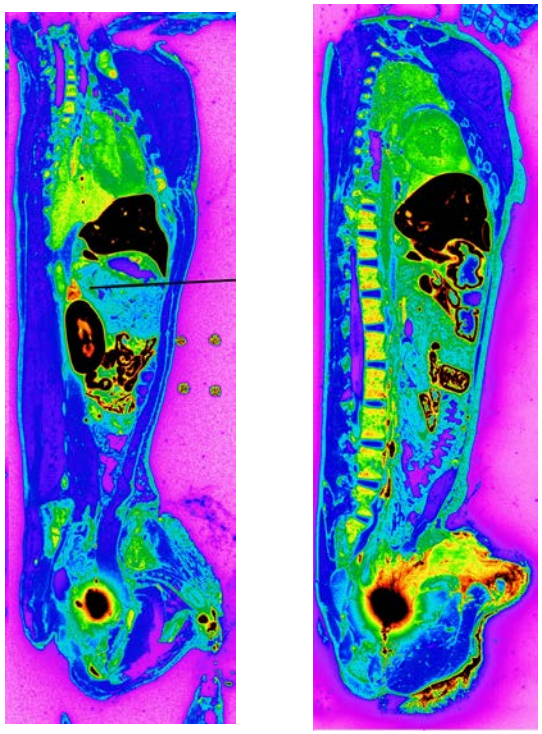
Targets HIR at BBB for CNS

IDUA domain

Targets M6PR for somatic

AGT-181

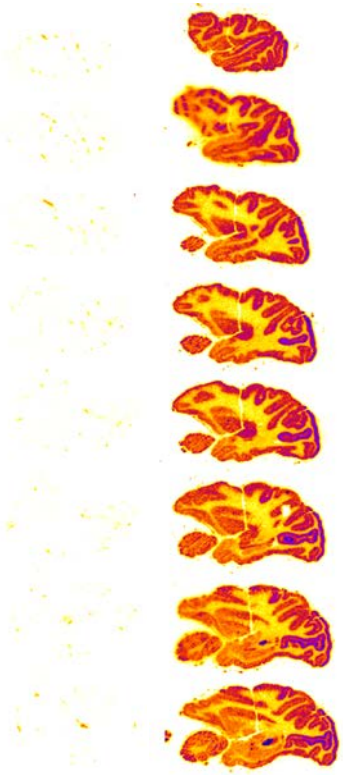
Somatic uptake in the Rhesus monkey



IDUA alone

AGT-181

Brain uptake in the Rhesus monkey



IDUA alone

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HIRMAb=monoclonal antibody (MAb) to human insulin receptor (HIR)

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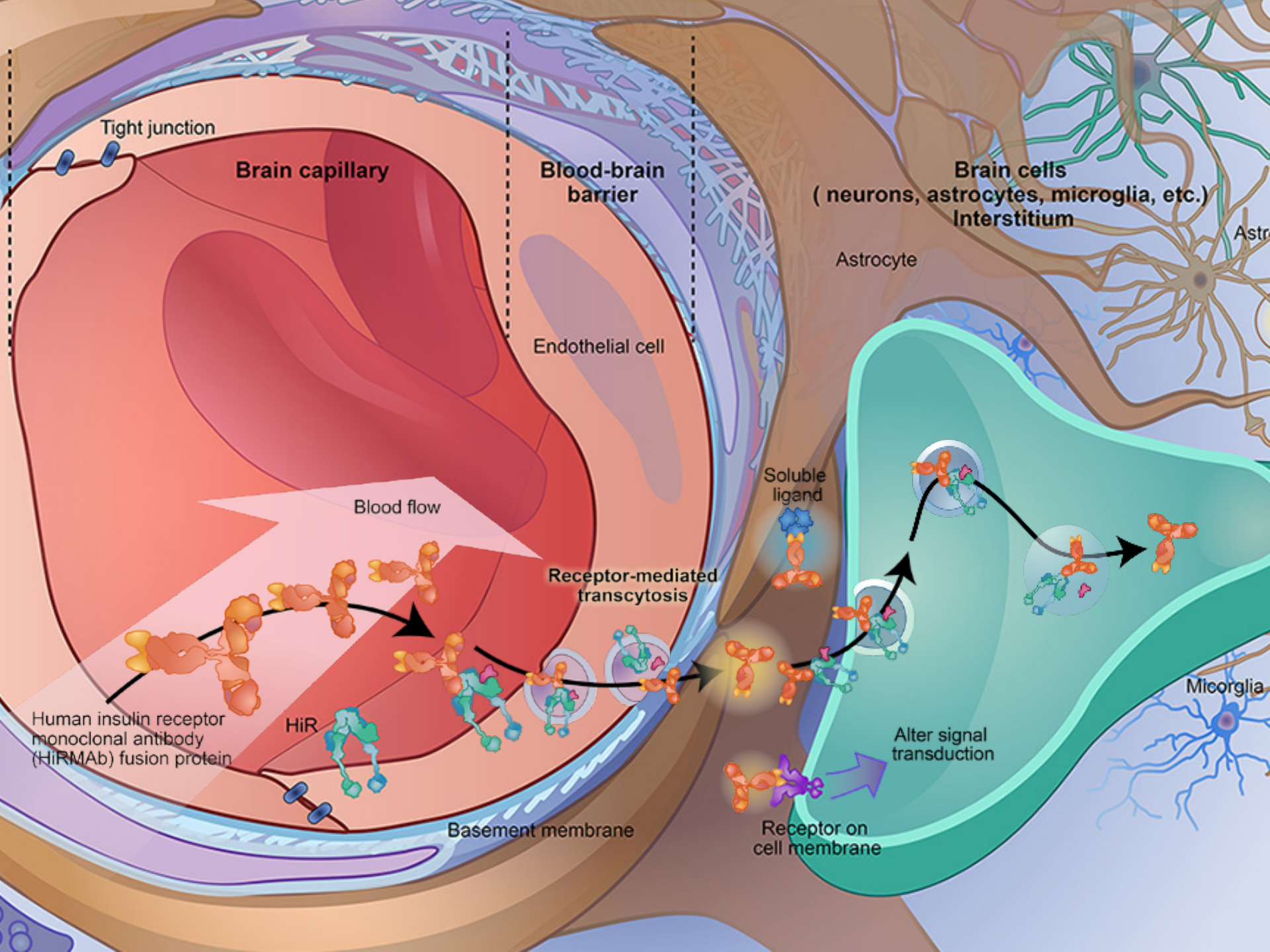
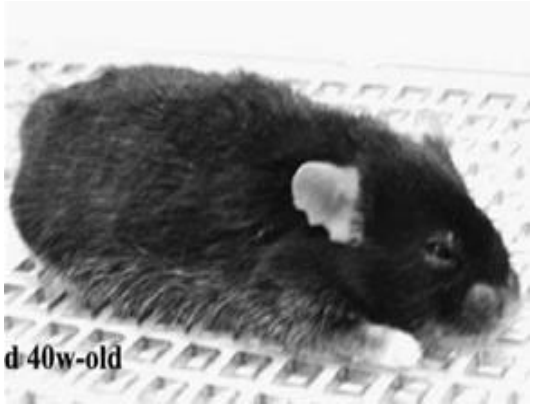

Tight junction
Brain capillary
Blood-brain barrier
Brain cells (neurons, astrocytes, microglia, etc.) Interstitium
Astrocyte
Endothelial cell
Soluble ligand
Blood flow
Receptor-mediated transcytosis
Human insulin receptor monoclonal antibody (HiRMAb) fusion protein
HiR
Alter signal transduction
Receptor on cell membrane
Basement membrane
Micorglia

Preclinical: Mouse model of MPS I (null for IDUA enzyme)

DISEASE	DEFICIENT ENZYME	STANDARD OF CARE
Hurler Syndrome (MPS I)	α–L-iduronidase (IDUA)	Aldurazyme® enzyme replacement therapy (ERT) administered weekly by IV

STUDY DESIGN	DOSE	CONCLUSION
Mouse with MPS I (age: 6 months)	AGT-m181 (1 mg/kg) administered 2 times per week by IV for 8 weeks	Reductions in: • Lysosomal inclusion bodies in brain • Glycosoaminoglycans in peripheral organs • Immune response

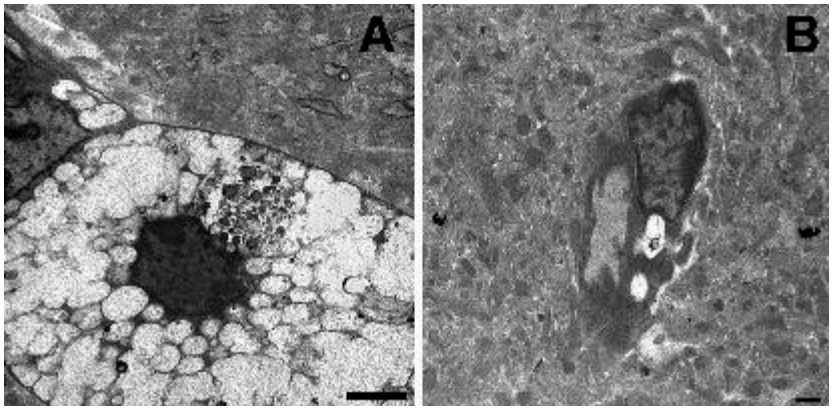


Reduction in GAGs in Peripheral Organs and in Brain in MPSI Mouse

Organ	Organ GAG (µg/mg protein)	
	Saline	AGT-m181
Liver	78 ± 7	< 2.5****
Spleen	50 ± 12	10 ± 3**
Kidney	47 ± 6	37 ± 3
Heart	35 ± 4	23 ± 3*
* p < 0.05, ** p < 0.01, **** p < 0.001		

Group	Number of Multi-vacuolated Brain Cells/100 Brain Cell Nucleoli
Saline	18.5 ± 1.1
AGT-m181	5.0 ± 1.6 **

Saline AGT-m181



Electron Microscopy shows Reduced Lysosomal Inclusion Bodies Following AGT-m181 Treatment

- Reductions in GAG levels in peripheral tissues comparable to laronidase in MPSI dog
- Lysosomal inclusions bodies in the brain reduced 73%

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AGT-181 Clinical Trials in MPSI:
Safety and Plasma Pharmacokinetics

Clinical Trials.ORG NCT	Country	Age	Phase	Status
02371226	US	adults	I	closed
03071341	Brazil	adults	I	closed
03071341	Brazil	children	II	Completed (6 mos)
03071341	Brazil	children	II	Extension (12 mos)

Summary

- ❑ Over 650 IV infusions of AGT-181 in 20 patients, including 11 children
- ❑ Incidence of mild hypoglycemia during infusion (50-70 mg%) is <5%
- ❑ Stable plasma glucose for 24 hrs after infusion with IV dosing of 0.3 to 6 mg/kg
- ❑ Incidence of infusion-related reactions requiring treatment is <5%
- ❑ Plasma pharmacokinetics (PK) of AGT-181 in children is comparable to laronidase
- ❑ Plasma PK of AGT-181 not affected by pre-existing anti-drug antibody (ADA) titers against laronidase

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AGT-181 Clinical Trial in Children in MPSI: *Somatic efficacy (6 months therapy)*

Preliminary results

- Stabilization/reduction in urinary glycosaminoglycans (GAGs) comparable to laronidase
- Improvement in shoulder range of motion (ROM) in all patients
- Reductions in liver and spleen volumes, even in patients previously on long-term laronidase treatment; reduction in liver volume of 35% in several patients

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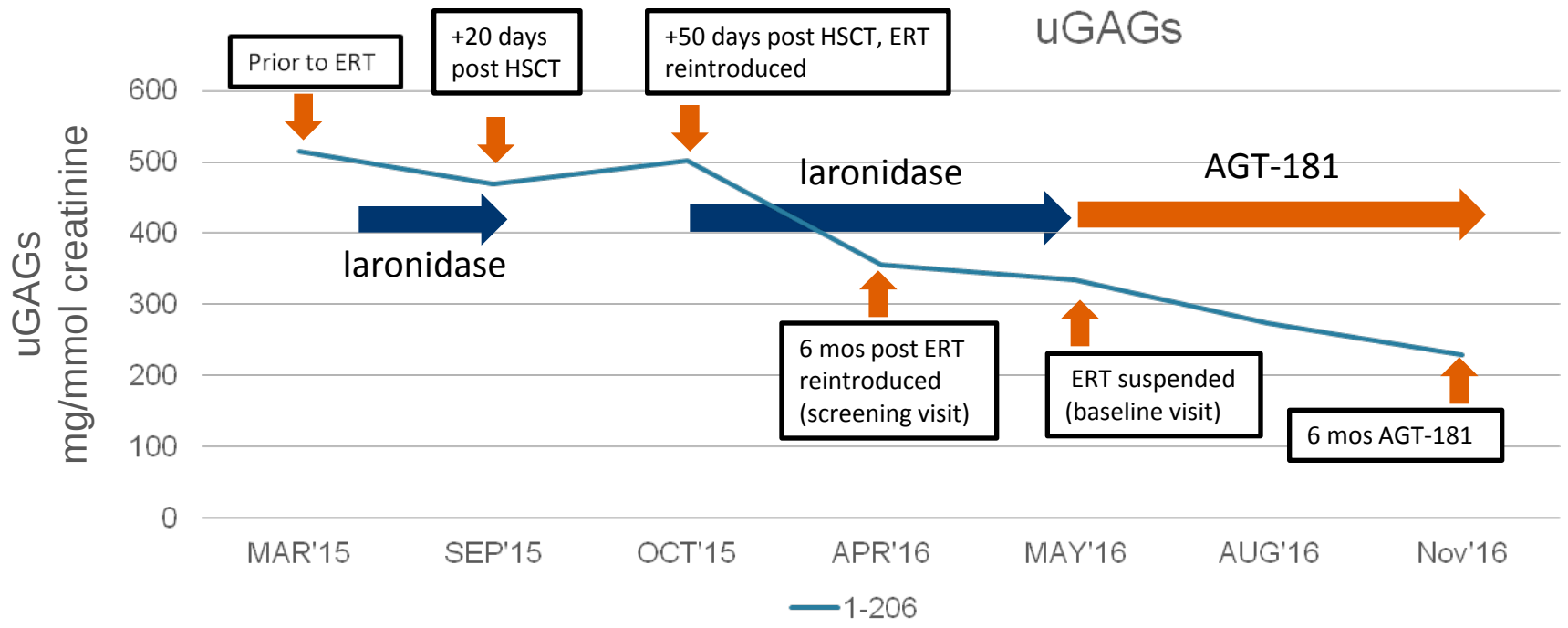
AGT-181-101: Subject 1-206

Modulation of uGAGs by ERT, HSCT, AGT-181



ERT: enzyme replacement therapy with laronidase
HSCT: hematopoietic stem cell transplant

AGT-181 Clinical Trial in Childen in MPSI: *CNS efficacy (6 months therapy)*

- IQ in children is measured as Developmental Quotient (DQ), where DQ is (age-equivalent score)/(chronologic age)*100
- DQ in children with age-equivalent score (AES) of <4 years is measured with Bayley Scales of Infant Development (BSID)
- DQ in children with AES>4 years measured with Kaufman Assessment Battery for Children (KABC)
- The 11 children in the Brazil study had severe mental retardation with a mean DQ of 32 at enrollment in the AGT-181 treatment trial

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AGT-181 Clinical Trial in Children in MPSI: Preliminary assessment of *CNS efficacy*

Bayley Scales of Infant Development (BSID)

- 5 Domains of testing: Cognition; Receptive Language; Expressive Language; Fine Motor skills; Gross Motor skills
- Age equivalent scores increased or stabilized in 90% of 5 domains in 8 children after 6 months of AGT-181 therapy

Kaufman Assessment Battery for Children (KABC)

- 5 Domains of testing: Conceptual; Face Recognition; Pattern Recognition; Triangles; Hand Movement
- Age equivalent scores increased or stabilized in 80% of 5 domains in 3 children with 6 months of AGT-181

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MRI volumetrics in children with MPSI after 6 months of treatment with AGT-181

- In general, structural changes in brain volumes are not detected with just 6 months of AGT-181 treatment
- Nevertheless, significant changes were observed in some patients
- A 40% reduction in the volume of the lateral ventricles was observed in one patient after 13 weeks of treatment, which stabilized at 26 weeks of treatment
- In a 15 year old, with cerebral atrophy, 6 months of treatment caused a 32% increase in cortical white matter volume and a 17% increase in total gray matter volume

Phase II Clinical Trial of AGT-181 in Children with Severe MPSI:
Summary

<u>On a somatic level</u>, AGT-181 exhibits a profile similar to existing ERT with laronidase:

- The overall safety and tolerability of AGT-181 is comparable to current Enzyme Replacement Therapy with laronidase
- Somatic effects included maintenance of low urinary GAG levels, as well as improvements in shoulder ROM and further reductions in liver and spleen volumes in patients previously on laronidase ERT for years

<u>On a cognitive level</u>, interim data indicate AGT-181 may improve and/or stabilize the cognitive deterioration in MPS-I patients

- Improvements or stabilization of neurological and cognitive function was observed in 90% of 5 domains tested in 8 children with BSID
- Improvements or stabilization of neurological and cognitive function was observed in 80% of 5 domains tested in 3 children with KABC

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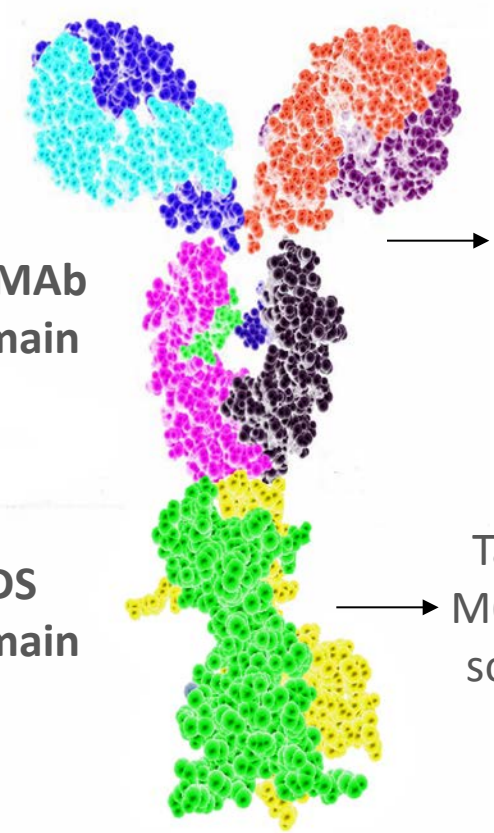
AGT-182 for Treatment of Brain in MPS-II (Hunter Syndrome):
HIRMAb-IDS fusion protein

HIRMAb-IDS fusion protein



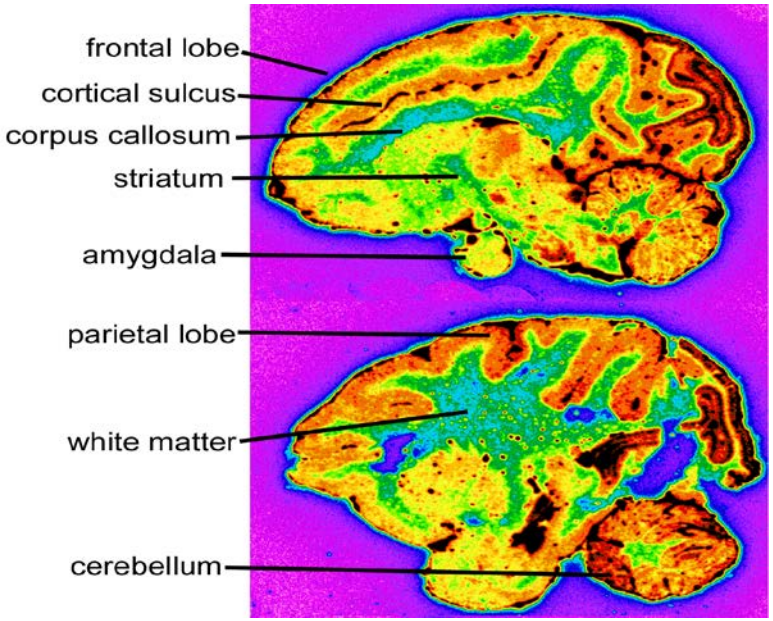
HIRMAb domain → Targets HIR at BBB for CNS

IDS domain → Targets M6PR for somatic

AGT-182

IDS=iduronate 2-sulfatase

Brain uptake in Rhesus monkey



Clinical Trials	
Phase I in adults NCT02262338 ArmaGen Completed	Phase II in children Shire 2017-18

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Thank You!