The SMSRF 5-Year Research Roadmap: From RAI1 Biology to Clinical Development

The Science Behind the Strategy

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We are at a pivotal point for Smith-Magenis Syndrome (SMS). Smith-Magenis Syndrome Research Foundation (SMSR)'s investments over the last several years have helped validate a critical premise: increasing RAI1 output can plausibly reverse key SMS deficits, making RAI1-focused therapies a credible disease-modifying north star. At the same time, translation remains high-risk, and SMS is meaningfully behind better-funded single-gene neurodevelopmental syndromes that already have multiple clinical programs. Our flagship McGill/Stanford program is progressing, but the core technical challenges remain brain-wide delivery and safety/expression control, and early timelines imply a multi-year runway to first-in-human.

The external environment is now turning in our favor. The community is increasingly becoming trial-ready, regulators are clarifying accelerated pathways for advanced therapies, and large platform funders are investing in genetic-medicine pipelines that can spill over into SMS. Delivery toolkits (viral and non-viral), manufacturing, and analytics are improving, and recent "N-of-few" precedents are making ultra-small studies more feasible.

Over the next five years, the strategic need is to (a) build an active outreach engine to recruit top researchers and partners specializing in activation, delivery, biomarkers, and clinical execution; (b) diversify funding via milestone guided programs; and (c) upgrade trial readiness through registry improvement to capture the natural history of the disorder. The north star for SMSRF is a first-in-human disease-modifying SMS trial by ~2030, while remaining modality-flexible and building near-term symptomatic wins in parallel if aligned with our organization's objectives.

Where We Are

Historically, SMSRF has funded basic science to understand SMS biology and to develop a gene therapy aimed at addressing key SMS phenotypes. This validated that increasing RAI1 expression can potentially reverse SMS deficits [1] and provided confidence that therapies designed to boost RAI1 in patients could generate a high impact, multi-targeted treatment. Of course, developing any new therapies is challenging. Industry analyses suggest only ~28% of rare disease gene therapies reaching Phase 1 eventually win approval [2] – but the successes in related syndromes provide a source of optimism. In disorders caused by a single missing gene, novel treatments are advancing at unprecedented pace. For context, Angelman syndrome (UBE3A gene) now has over a dozen programs in development (at least 3 therapies in Phase 3 trials) [3], and Rett syndrome (MECP2 gene) has 20+ therapeutic candidates being pursued across industry [5] (including one FDA-approved drug in 2023). In comparison, SMS currently has no disease-modifying treatments in trials, underscoring both the gap and the urgency for SMSRF to accelerate translational research. SMSRF's flagship gene therapy project (a collaboration with McGill/Stanford) is in progress, but estimates provided by McGill earlier this year were pointing to ~5+ years from a first-in-human trial. Given the precedent of other gene therapies in rare pediatric disorders, the odds are improving such that once in clinical trials, gene therapies for rare diseases have shown higher success rates than conventional drugs [2]. The hurdles for our RAI1 program will, however, remain 1) achieving efficient brain-wide delivery and, 2) ensuring safety (avoiding overexpression).

Momentum
Despite being behind other rare diseases in the race for effective, system-wide treatments, SMS research can now capitalize on the momentum generated by recent favorable trends in science, regulation, and funding:

a) **Increasing trial readiness**: After years of groundwork, the SMS patient community is more organized than ever. A PRISMS-led patient registry is active and growing, capturing natural history data. There is a global network of families, open trials, and clinicians increasingly aware of SMS. Importantly, the registry is planning an overhaul, and SMSRF is considering becoming a partner in that effort - both to strengthen data quality/coverage and to ensure its maximal utility for future interventional studies. This level of organization is something lacking from many nascent rare disease efforts. It means when we approach partners or funders, we can credibly show that SMS is "trial-ready" with a defined patient cohort, baseline data, and a committed foundation to support recruitment and advocacy.

b) **New favorable regulations:** In September 2025, FDA published a draft for updated guidance on expedited programs for regenerative medicine therapies (RMAT), outlining how cell and gene therapy sponsors can engage early with the Center for Biologics Evaluation and Research (CBER) and leverage programs such as RMAT.[12] Separately, Congress is showing momentum to restore the Rare Pediatric Disease Priority Review Voucher (PRV[KD2]) program: the U.S. House unanimously passed reauthorization legislation in December 2025 (final enactment pending) [13]. If SMS therapy ultimately qualifies and is approved, a PRV could be sold or used for priority review of another product; disclosed PRV sale prices in recent years have commonly fallen around $100–$160M [14].

c) **Clinical precedents for "N-of-few" therapies:** In 2023-2025, the first personalized gene-editing treatments were given to individual children under compassionate use, and FDA is actively working on frameworks for personalized therapies. At Children's Hospital of Philadelphia, a custom CRISPR base edit was created and administered to an infant under 12-months of age who had a fatal metabolic disorder [16]. This was a landmark case that normalized the concept of ultra-small trials or even single-patient "trials" for rare diseases.

d) **More money for rare disorders:** Major initiatives have launched targeting the price niche SMS occupies: rare pediatric genetic diseases. For example, in July 2025 the Chan Zuckerberg Initiative (CZI) and UC Berkeley's IGI announced a $20M Center for Pediatric CRISPR Cures, specifically to develop personalized CRISPR therapies for children with rare genetic disorders [15]. This came on the heels of the first successful "N-of-1" CRISPR therapy in a child, proving such custom-made approaches can work [16]. Similarly, the U.S. government's new agency, the Advanced Research Projects Agency for Health (ARPA-H) is investing heavily in enabling technologies: their THRIVE program (opened Oct 2025) aims to create platform technologies for in vivo precision genetic medicines (PGMs) to cure rare diseases [17], emphasizing affordability and scalability. ARPA-H's FRONT program (launched 2025) is pushing radical brain repair technologies (like regenerating neural tissue). Although focused on injuries, it drives innovation in CNS delivery and circuit restoration that could benefit SMS indirectly [18]. On top of these, NIH's BRAIN Initiative and other neurobiology funders continue pouring money into tools for mapping and modulating neural circuits, which could help define biomarkers and outcomes for SMS.

e) **Better delivery systems for the brain:** A perennial challenge for genetic therapy in SMS is getting the treatment to the right cells safely. We might no longer be limited to the classic Adeno-Associated Virus (AAV) vectors. Recent research shows blood–brain barrier-crossing capabilities in novel viral vectors and lipid nanoparticles (LNPs). Non-viral methods, ligand-targeted nanoparticles, and refined AAVs are expanding the toolkit for CNS delivery [18] [20]. By the time SMSRF is ready for human trials, we may be able to choose from improved vectors or even LNP based delivery of gene editors that reach the brain with less immunogenic risk. Additionally, manufacturing and analytics for gene therapies are becoming more standardized as the field matures, lowering barriers for small organizations to enter clinical development with a viable product.

f) **Artificial Intelligence and brain atlases accelerating research:** The convergence of AI and big data in neuroscience is providing unprecedented insight into brain development. In late 2025, an international consortium published the first draft atlas of the developing human brain, mapping how 5,000+ cell types form and connect from embryo to adult [23]. These atlases (part of NIH's Brain Initiative Cell Atlas Network, BICAN) chart gene expression and cell maturation timing across brain regions. Such knowledge is extremely relevant to SMS: it helps pinpoint when and where RAI1 is needed, and when intervention might yield the greatest benefit. The atlas data, combined with machine learning, will help us identify biomarkers and optimal therapeutic windows. For example, if AI analysis shows RAI1 is crucial at a certain developmental stage for myelination or synapse formation, we can ensure our trials measure endpoints around those functions. Moreover, major funders like the Chan Zuckerberg Initiative (CZI) are investing in AI-powered biology and cellular mapping tools [24]. As a result, the next few years should bring even more refined maps of neuronal circuits and gene networks. Ultimately, this could allow for precision design of SMS treatments (targeting the right brain circuits) and detecting treatment effects with digital biomarkers.

Therapeutic Options in View

There are a limited number of plausible paths for disease-modifying therapies in SMS:

- **Gene/epigenetic activation (CRISPRa and related regulators):** targeted activators that increase RAI1 output from the native locus without changing the DNA sequence, with the added advantage of titrated expression-control concepts in the broader activation toolkit. This is the modality most directly supported by SMS-specific data today and is what McGill and potentially Yale are focusing on.
- **RNA/translation boosting:** these approaches increase protein output from existing transcripts (e.g., translation-enhancement concepts like SINEUP-style RNAs or ASO through TANGO [25]) are still in preliminary but could complement other strategies if validated.
- **Gene replacement (classic AAV-style):** conceptually straightforward for monogenic disease, but technically heavier in the context of SMS because of RAI1's size/isoforms and the need for tight expression control. This is still worth monitoring as theoretical solutions for these obstacles exist (e.g. minigene, dual-vector, or cell-selective promoter strategies).

In parallel, there are pragmatic symptom-domain levers that can improve quality of life now and reduce confounders in future interventional studies. Historically, this is not where SMSRF has concentrated its effort. Leaning in here would represent a deliberate pivot (and likely a different mix of partners, trial designs, and timelines). Some of these newer strategies include:

- **Drug repurposing opportunities:** systematic evaluation of existing drugs that target downstream pathways (attention/impulsivity, irritability/aggression, sleep architecture, metabolic tone, etc.). This strategy can yield faster symptomatic wins while RAI1-directed programs mature. This can be accelerated by partnering with groups that are explicitly built for repurposing existing pharmaceuticals and rapid indication expansion. Examples include Healx (AI-driven rare-disease repurposing) and, SOM Biotech (repurposing-focused, with an orphan/CNS emphasis).
- **Neuromodulation:** non-invasive approaches (e.g., photo-biomodulation such as red/near-infrared light, and other emerging neuromodulation techniques) could be explored via focused pilots in defined symptom domains (sleep/arousal, attention, irritability) with clear endpoints.
- **Metabolic / oxidative stress mitigation:** low-risk repurposing and supportive strategies (e.g., antioxidants such as N-acetylcysteine (NAC)) can be evaluated in small pilots as symptomatic adjuncts (evidence strength varies by domain).
- **Hyperphagia / obesity management**: beyond satiety-pathway agents, GLP-1 class medications are a practical option to consider for weight and appetite control. Interestingly, a single case study of subcutaneous delivery of a GLP-1 receptor agonist in an 18-year-old with SMS demonstrated measurable weight loss with concurrent reduction of impulsive behaviors. This auxiliary outcome provides potential for elucidating a common underlying foundation for weight gain and impulsivity in SMS, paving the way for new reverse phenotyping initiatives in SMS.

Where Should We Go

With multiple plausible therapeutic avenues to consider, alongside clearer external momentum and a growing sense of how to make SMS "trial-ready", the key questions are no longer tethered to whether progress is possible, but 1) where SMSRF should allocate its finite funding resources first, and 2) how to prioritize projects with reasonable likelihood of success that can be achieved in relatively short timeline. The next section lays out a practical execution plan to address these complementary priorities:

Proactive outreach - Actively engage leading labs focused on gene activation and other transcriptional control approaches that could boost RAI1 from the intact allele while pulling in teams with proven track records in neuronal gene regulation and clinically oriented platform work.

- **Learn from adjacent playbooks:** Recruit investigators from disorders with close modality overlap (e.g., Angelman, Rett, and other monogenic neurodevelopmental disorders (NDDs)) where platforms for upregulation, gene activation, or gene therapy translation have already been stress-tested. This will allow the reuse of principles, assays, and safety frameworks rather than reinventing them for SMS.
- **Delivery and translational neuroscience leaders:** Build a short list of researchers with deep CNS delivery expertise and recruit them early to shape feasibility and de-risk Investigational New Drug (IND)-enabling plans.
- **Clinical trial leadership early, not late:** Bring in trial-experienced clinicians and sites who have run related NDD trials to help define endpoints, inclusion criteria, and operational feasibility from day one - so "trial readiness" isn't an afterthought.

Funding and execution to support that outreach engine (next 5 years)

- **Move to milestone-based awards:** Evolve from scattered small grants to larger, goal-oriented, milestone-gated funding with clear go/no-go criteria (e.g., "RAI1 activation," "CNS delivery," "biomarkers"), plus seed awards to attract new labs into SMS.
- **Partner-ready packaging:** Position SMS as a well-characterized monogenic disorder with an organized patient community and clear therapeutic hypotheses - ideal for platform groups looking to demonstrate clinical relevance.
- **Balance cure-path with near-term impact:** In parallel, investigate funding high-confidence symptomatic/repurposed interventions that can improve quality of life sooner and strengthen measurement infrastructure for future disease-modifying trials.
- **Grow the field intentionally:** Create New Investigator awards, cross-disciplinary pilots, and shared resources (models, cell lines, protocols, data access) to lower barriers and increase the number of credible SMS contributors.

Make "trial readiness" real through an IND-grade registry

- **Continue strengthening natural history and readiness assets**: Expand enrollment (including globally, where feasible), increasing longitudinal follow-up (behavior, sleep, milestones), improving usability for families, and enabling responsible data sharing to stimulate publications and partner interest.

North Star timeline

- **This strategy supports a first-in-human Phase 1/2 disease-modifying SMS trial by 2030**: Namely, animal proof-of-concept around 2027, IND-enabling studies 2028–29, IND submission 2029, and first dosing 2030 - while staying flexible on modality (e.g. gene activation/epigenetic editing, gene therapy, or an alternative upregulation approach if it becomes the best path).

Funding and Development Scenarios

	Baseline (status quo)	Growth (expanded effort)	High Growth (max acceleration)
Annual budget (5y total)	~$250K/yr (~$1.25M)	~$500K/yr (~$2.5M)	~$1M/yr (~$5M)
Portfolio strategy	1 lead program + small adjuncts	2 parallel therapy shots on goal	3+ programs
Key 2026–2027 outcomes	gene therapy PoC in animals by ~2027	In vivo efficacy for 2 approaches by ~2027; early FDA touchpoints possible	Strong preclinical results across programs; start IND-enabling (tox/biodistribution) + pilot GMP early
Key 2028–2030 outcomes	If successful IND-enabling begins ~2028; IND ready to file by ~2029; Phase 1/2 starts ~2030 (limited sites)	IND filed ~2029 (or late ~2028 stretch); multi-site trial fully prepared; backup program kept warm	IND filed by ~2028; first dosing potentially ~2029; by 2030 multiple trials possible

Key Foundational SMS References

The SMSRF 5-Year Research Roadmap is built upon more than two decades of scientific discovery that have transformed Smith–Magenis syndrome (SMS) from a clinically described disorder into a biologically understood condition with emerging therapeutic opportunities. Collectively, these discoveries have helped shift SMS research from primarily describing symptoms to understanding the underlying biology of the disorder. This transition forms the scientific basis for SMSRF's 5-Year Research Roadmap and our goal of advancing disease-modifying therapies toward human clinical trials. The following publications and resources provide the foundation for much of what is known about SMS today:

1. GeneReviews®: Smith–Magenis Syndrome

Smith–Magenis Syndrome. GeneReviews®, University of Washington, Seattle.

The most comprehensive clinical and scientific reference on SMS, covering genetics, diagnosis, clinical features, management, inheritance, sleep disturbances, behavioral characteristics, and emerging research directions. Widely regarded as the primary reference for clinicians and researchers entering the field.

2. Slager RE, Newton TL, Vlangos CN, Finucane B, Elsea SH.

Mutations in RAI1 associated with Smith–Magenis syndrome. *Nature Genetics.* 2003;33:466–468.

A landmark study establishing that mutations in the RAI1 gene can independently cause SMS, helping identify RAI1 as the principal dosage-sensitive gene underlying the syndrome.

3. Elsea SH, Girirajan S.

Smith–Magenis Syndrome. *European Journal of Human Genetics.* 2008;16:412–421.

A foundational review summarizing the genetics, clinical presentation, molecular mechanisms, and biological understanding of SMS that helped frame the modern view of the disorder.

4. RAI1 Restoration Studies

Recent SMSRF-supported research has demonstrated that restoring RAI1 expression can improve key disease-related phenotypes in SMS animal models. These studies provide some of the strongest evidence to date that SMS biology may be modifiable and that RAI1-focused therapies represent a credible therapeutic strategy.

5. Emerging Proteostasis and Gene-Dosage Research

Recent studies identifying regulators of RAI1 protein stability—including TRIM27-mediated degradation pathways—have expanded the range of potential therapeutic approaches beyond traditional gene replacement strategies.

Together, these findings suggest that increasing functional RAI1 activity may be achievable through multiple therapeutic modalities.