

A Cluster of Nontuberculous Mycobacterial Tenosynovitis Following Hurricane Relief Efforts

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Background. Nontuberculous mycobacteria (NTM) are a rare cause of infectious tenosynovitis of the upper extremity. Using molecular methods, clinical microbiology laboratories are increasingly reporting identification down to the species level. Improved methods for speciation are revealing new insights into the clinical and epidemiologic features of rare NTM infections.

Methods. We encountered 3 cases of epidemiologically linked upper extremity NTM tenosynovitis associated with exposure to hurricane-damaged wood. We conducted whole-genome sequencing to assess isolate relatedness followed by a literature review of NTM infections that involved the upper extremity.

Results. Despite shared epidemiologic risk, the cases were caused by 3 distinct organisms. Two cases were rare infections caused by closely related but distinct species within the *Mycobacterium terrae* complex that could not be differentiated by traditional methods. The third case was caused by *Mycobacterium intracellulare*. An updated literature review that focused on research that used modern molecular speciation methods found that several species within the *M. terrae* complex are increasingly reported as a cause of upper extremity tenosynovitis, often in association with environmental exposures.

Conclusions. These cases illustrate the importance of molecular methods for speciating phenotypically similar NTM, as well as the limitations of laboratory-based surveillance in detecting point-source outbreaks when the source is environmental and may involve multiple organisms.

Keywords. *Mycobacterium arupense*; *Mycobacterium heraklionense*; *Mycobacterium terrae* complex; *Mycobacterium intracellulare*; tenosynovitis.

Nontuberculous mycobacteria (NTM) are environmental organisms of varying pathogenicity that have been associated with a wide variety of infections, primarily subacute and chronic in nature. While a number of reports have described isolation of the same organism from the environment as the patient [1], exposure to these organisms is probably a constant occurrence [2], and infection requires a combination of environmental factors (eg, high organism load in hot tub aerosols) [3], exposure factors (eg, inoculation via surgical incisions or injection) [4], and host factors (eg, genetic susceptibility, immunosuppression) [5]. Tenosynovitis is an uncommon manifestation of NTM infection, most commonly caused by *Mycobacterium marinum* or *Mycobacterium avium-intracellulare* complex [6, 7].

Here, we report 3 epidemiologically linked cases of tenosynovitis that originated from handling hurricane-damaged wood. While all

3 cases arose from the same source, they were caused by 3 distinct species. Two of these species were very closely related, falling within the *Mycobacterium terrae* complex, which is a rare cause of tenosynovitis [8]. In addition, a third case from the same source that involved the more commonly reported *M. avium-intracellulare* complex was identified. These 3 cases demonstrate both the importance of molecular methods for differentiating closely related and phenotypically similar species and the need for enhanced detection mechanisms for polymicrobial infection clusters.

Case 1

A 60-year-old male with seronegative rheumatoid arthritis presented with chronic tenosynovitis of the left hand. At the time of initial presentation, he had been receiving infliximab and methotrexate for more than 1 year for his rheumatoid arthritis. He first developed slowly progressive swelling of his left index finger after pricking the same finger with a splinter while handling water-damaged plywood during hurricane relief efforts after Hurricane Matthew. Initial attempts to find and remove a foreign body were unsuccessful. An empiric attempt at treating for possible trigger finger with 2 local corticosteroid injections was similarly unhelpful. Nearly 7 months after his initial injury, the swelling of his left index finger persisted, at which point

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magnetic resonance imaging (MRI) of the hand revealed flexor tenosynovitis with rice bodies in the flexor compartment. He underwent operative debridement, with histopathology confirming chronic granulomatous inflammation of the resected synovium. Tissue cultures eventually grew a slow-growing mycobacterium with phenotypic features suggestive of *M. terrae* complex. Empiric treatment with azithromycin, ethambutol, and rifampin was started promptly after surgery, and his immune-suppressive regimen was modified to methotrexate and abatacept. Final speciation by 16S rRNA sequencing confirmed *Mycobacterium arupense*. Susceptibility testing obtained through the University of Texas Health Science Center indicated low minimum inhibitory concentrations to clarithromycin (1 g/mL). He completed 12 months of azithromycin, rifampin, and ethambutol with full clinical resolution.

Case 2

During the initial clinic visit with case 1, he mentioned that a nongenetically related family member who had worked on the same relief effort, at the same site, had “the same infection I do.” This information resulted in contact between the physicians caring for case 1 and case 2. The second case was a 66-year-old male with coronary artery disease, nephrolithiasis, and hypertension who developed chronic swelling of his right small (fifth) finger in the months following cleanup work during hurricane relief efforts after Hurricane Matthew. He underwent initial carpal tunnel release without benefit. An MRI was performed after 6 months of progressive swelling of the hand, confirming tenosynovitis of the flexor tendons. He proceeded to operative debridement, with histopathology revealing chronic inflammation, including giant cells. Cultures eventually grew NTM consistent with *M. terrae* complex. He was treated with azithromycin, linezolid, and doxycycline but eventually had to transition from linezolid to levofloxacin due to gastrointestinal upset with the linezolid. He completed 6 months of therapy with full clinical resolution.

Case 3

As cases 1 and 2 were completing treatment, a third unrelated patient was referred to the clinic with chronic tenosynovitis and a history of participation in hurricane relief efforts. The patient, a 71-year-old male with recently diagnosed uncontrolled diabetes mellitus, developed chronic progressive swelling in his right hand that lasted for more than 6 months. He was a retired carpenter who volunteered with home repair efforts following Hurricane Matthew, including extensive removal of water-damaged wooden floorboards. He rarely wore gloves and suffered multiple splinters and superficial cuts to his hands and fingers. He had been treated empirically for trigger finger with local steroid injections and later carpal tunnel release without improvement. He had persistent swelling and tenosynovitis that eventually required operative debridement, with cultures

confirming *Mycobacterium intracellulare*. He was treated with azithromycin, ethambutol, and rifampin along with an initial 12 weeks of amikacin. Six months into a planned 12-month course of therapy, he had full clinical resolution.

METHODS

With 3 cases of a rare infection occurring among epidemiologically linked patients, we next conducted whole-genome sequencing on the clinical isolates from case 1 and case 2 to determine whether they were genetically related. Genomic DNA libraries were prepared using a DNA-seq kit. Sequencing was performed with Illumina MiSeq using 150 bp paired end reads. Adapter sequences were removed with CutAdapt v2.3, and the trimmed reads were assembled with SPAdes 3.5. The resulting contigs were then aligned with draft genomes for a number of sequenced NTM genomes using a Burrows-Wheeler transform-based algorithm [9]. Phylogenetic trees were constructed from a concatenated alignment of single-nucleotide polymorphisms using CSI Phylogeny 1.4, with *Mycobacterium celatum* serving as an outgroup [10]. Phylogenetic trees were visualized using FigTree v 1.4.4. Sequences were deposited to the National Center for Biotechnology Information Sequence Read Archives under accession numbers SRR12540232 (North Carolina isolate) and SRR12540231 (South Dakota isolate), BioProject PRJNA659999.

RESULTS

Initial rRNA sequencing results from case 1 revealed 100% identity with *M. arupense* type strain (American Type Culture Collection BAA-1242). Next, we performed whole-genome sequencing of both strains from case 1 and case 2 and found that although sequencing reads from the case 1 isolate mapped consistently to a draft *M. arupense* genome (GenBank accession number LASW00000000), the case 2 isolate reads did not. Based on this finding, we compared the case 2 isolate with other *M. terrae* complex strains reported to have caused tenosynovitis (Table 1). Read mapping to available whole-genome sequences revealed a close match to *Mycobacterium heraklionense* strains. The case 3 isolate was confirmed as belonging to *M. avium-intracellulare* complex by both nucleic acid hybridization assay (AccuProbe) and 16S sequencing. Already being clearly unrelated to isolates 1 and 2, further speciation was not pursued.

To further understand the relationship of these strains to each other and to other NTM, we performed de novo assembly of each genome and compared them to all deposited whole-genome sequences from the *M. terrae* complex. Phylogenetic analysis placed each isolate in a distinct clade (Figure 1). The case 1 isolate was most closely related to the *M. arupense* strain DSM 44 942, while the case 2 isolate was most closely related to the *M. heraklionense* strain Davo (Figure 1). The case 3 isolate fell within the entirely separate *M. avium* complex (Figure 1).

Table 1. Summary of Recently Reported Cases of *Mycobacterium terrae* Complex and *Mycobacterium avium* Complex Tenosynovitis of the Hand

Location, Date, Reference	Species	Speciation Method	Clinical Summary	Immune Suppression	Exposure History	Treatment	Surgery	Outcome
United States, 2016 [11]	<i>M. heraklionense</i>	<i>rpoB</i> sequencing	72-year-old male	None (received local corticosteroid injections as initial treatment)	Gardening	Azithromycin+ Rifampin+ Ethambutol Duration: 2–3 months	Yes	Favorable (at 3 months)
United States, 2014 [12]	<i>M. heraklionense</i>	16S sequencing	37-year-old male	None	Tree pruning	Azithromycin+ Rifampin+ Ethambutol Duration: 3 months	Yes	Recurrence (at 3 months)
United States, 2016 [13]	<i>M. arupense</i>	Unspecified	62-year-old male	NK-cell deficiency, hyper interleukin-6, relapsing polychondritis Canakinumab+ IVIg+ Prednisone, 42.5 mg/d	None noted	Clarithromycin+ Ethambutol+ Rifabutin Duration: 12 months	Yes	Favorable (at 12 months)
Taiwan, 2008 [14]	<i>M. arupense</i>	Partial sequencing of 16S, <i>hsp65</i> , and <i>rpoB</i>	54-year-old female	Diabetes mellitus	Preceding motor vehicle accident	Clarithromycin + Moxifloxacin+ Rifabutin+ Ethambutol Duration: 6 months	Yes	Favorable
Japan, 2011 [15]	<i>M. arupense</i>	DNA hybridization	68-year-old male	None (received local corticosteroid injections as initial treatment)	None noted	Rifampin+ Ethambutol Duration: 14 months (including 4-month interruption)	Yes	Favorable (at 36 months)
France, 2012 [16]	<i>M. arupense</i>	16S and <i>hsp65</i> sequencing	35-year-old male	None (received local corticosteroid injections as initial treatment)	Penetrating hand injury	Clarithromycin+ Rifampin+ Ethambutol+ Amikacin (later clarithromycin + ciprofloxacin) Duration: 12 months total (amikacin and ethambutol for only 2 months)	Yes	Favorable
Korea, 2014 [17]	<i>M. arupense</i>	16S and <i>hsp65</i> sequencing	56-year-old female	Low-dose prednisone for hypopituitarism (received local corticosteroid injections as initial treatment)	Puncture injury from crab	Clarithromycin+ Rifampin+ Ethambutol Duration: not reported	Yes	Favorable
United States, 2014 [18]	<i>M. arupense</i>	16S sequencing	58-year-old male	Corticosteroids+ Adalimumab+ Methotrexate	Cattle farm, blunt trauma	Clarithromycin+ Rifampin+ Ethambutol Duration: 12 months	Yes	Favorable
Korea, 2020 [19]	<i>M. virginense</i>	<i>rpoB</i> sequencing	68-year-old female	None	Acupuncture	Clarithromycin Duration: 3 months	Yes	Favorable
United States, 2019 [20]	<i>M. avium</i> complex	Not specified	51-year-old male	Human immunodeficiency virus Type II diabetes mellitus	None reported	Clarithromycin+ Rifabutin+ Ethambutol Duration: 3 months	Yes	Favorable (at 5 years)

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Table 1. Continued

Location, Date, Reference	Species	Speciation Method	Clinical Summary	Immune Suppression	Exposure History	Treatment	Surgery	Outcome
United States, 2004 [21]	<i>M. avium</i> -complex	Not specified	44-year-old male	None	None noted	Clarithromycin+ Rifabutin+ Ethambutol Duration: 11 months	Yes	Favorable (at 12 months)
United States, 2006 [22]	<i>M. intracellulare</i>	Not specified	65-year-old male	None	None noted	Cycloserine+ Rifampin+ Levofloxacin Duration: 6 months	Yes	Favorable (at 6 months)
Belgium, 2000 [23]	<i>M. intracellulare</i>	16S sequencing	55-year-old female	Diabetes mellitus	None noted	Clarithromycin+ Rifampin+ Ethambutol Duration: 5 months	Yes	Recurrence 4 months after initial treatment
Korea, 2011 [24]	<i>M. intracellulare</i>	Not specified	63-year-old female	None	Prior carpal tunnel surgery	Clarithromycin+ Rifampin+ Ethambutol Duration: 16 months	Yes	Chronic wrist pain (still on therapy at time of report)
Japan, 2018 [25]	<i>M. intracellulare</i>	Not specified	71-year-old female	Rheumatoid arthritis Infliximab	None	Clarithromycin+ Rifabutin+ Ethambutol Duration: 18 months	Yes	Favorable (at 18 months)
Japan, 2016 [26]	<i>M. intracellulare</i>	Not specified	76-year-old male	Diabetes mellitus	Prior dog bite	Clarithromycin+ Rifampin+ Ethambutol Duration: not specified	Yes	Favorable (still on therapy)
Taiwan, 2014 [27]	<i>M. intracellulare</i>	Not specified	76-year-old male	None	None noted	Clarithromycin+ Rifampin+ Ethambutol Duration: 12 months	Yes	Favorable (at 18 months)
United States, 2020 (current study)	<i>M. arupense</i>	16S sequencing and whole-genome sequencing	60-year-old male	Rheumatoid arthritis Methotrexate+ infliximab	Injury while handling water-damaged plywood	Azithromycin+ Rifampin+ Ethambutol Duration: 12 months	Yes	Favorable (at 12 months)
	<i>M. heraklionense</i>	16S sequencing and whole-genome sequencing	66-year-old male	None	Injury while handling water-damaged plywood	Azithromycin+ Doxycycline+ Linezolid (linezolid changed to levofloxacin for gastrointestinal upset) Duration: 6 months	Yes	Favorable (at 6 months)
	<i>M. avium-intracellulare</i> complex	16S sequencing/DNA hybridization	71-year-old male	Diabetes mellitus	Injury while handling water-damaged plywood	Azithromycin+ Rifampin+ Ethambutol+ Amikacin Duration: 12 months	Yes	Favorable (at 6 months)

Abbreviations: IVIg: intravenous immunoglobulin; NK: natural killer.

Thus, the isolates, while epidemiologically linked, represented infections by distinct species within the *M. terrae* and *M. avium-intracellulare* complexes. Consistent with our whole-genome findings, we mapped reads from the case 2 isolate onto the *M. heraklionense* type strain (National Type Culture Collection [NCTC] 13432) rRNA and found 100% identity.

DISCUSSION

Here, we describe the use of molecular methods to distinguish between 2 closely related species within the *M. terrae* complex that caused 2 cases of tenosynovitis after exposure to a post-hurricane environment. In addition, a third case linked to hurricane-damaged wood is reported that arose from an

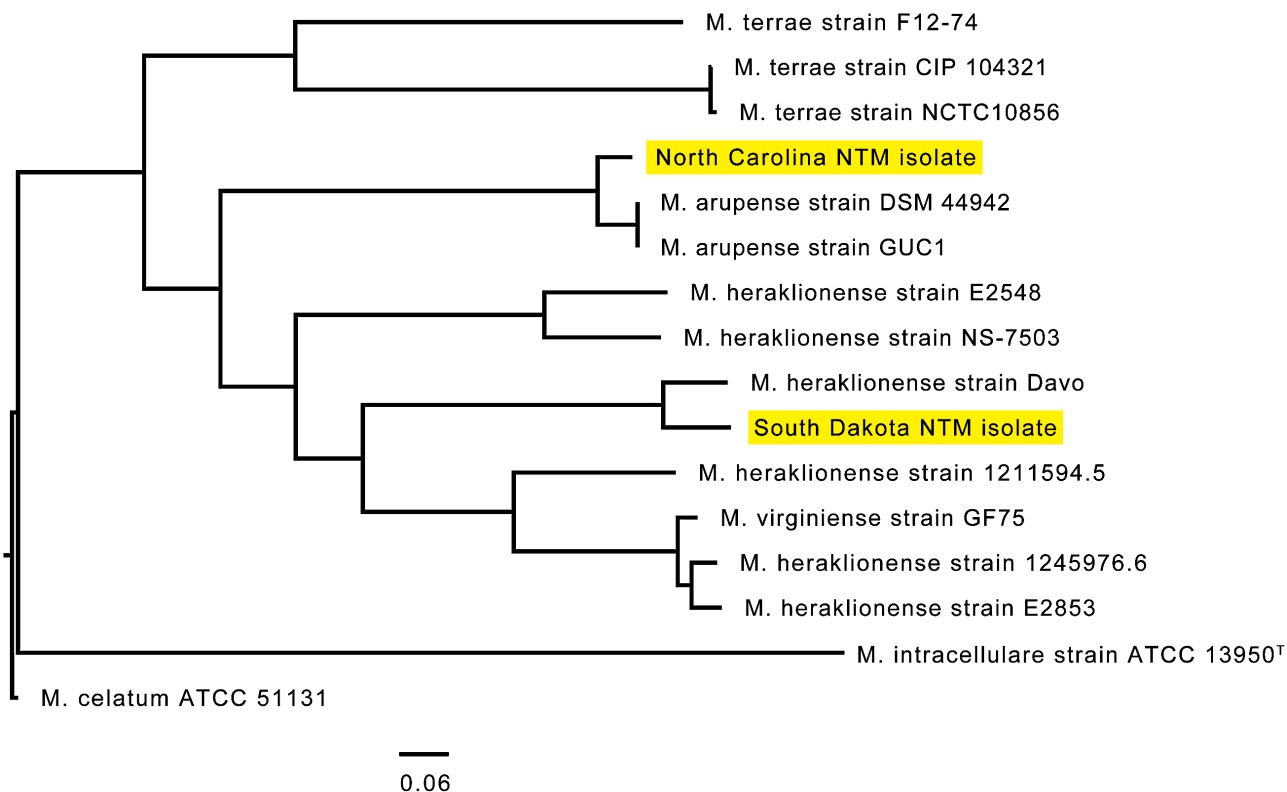


Figure 1. Phylogenetic tree constructed from single-nucleotide polymorphisms (SNPs) identified by whole-genome sequencing. Available whole-genome sequences from *Mycobacterium terrae* group members were compared to the newly assembled genomes of the case 1 and case 2 isolates. Phylogenetic analysis was performed with CSI Phylogeny 1.4, using *Mycobacterium celatum*, an NTM species that is outside of the *M. terrae* complex, as an outgroup. The results of the phylogenetic analysis were visualized using FigTree v 1.4.4. Scale bar indicates phylogenetic distance by SNPs per site. Abbreviations: ATCC, American Type Culture Collection; NTM, nontuberculous mycobacteria.

entirely different NTM in the *M. avium-intracellulare* complex. Without the shared experiences of the 3 patients, this case cluster would not have been detected. Furthermore, traditional clinical methods would not have differentiated between the *M. terrae* complex isolates.

Accurate speciation of NTM can be challenging. Many species share highly similar 16S rRNA sequences, limiting identification to clusters of more recently diverged species. For example, *M. avium-intracellulare* complex contains a number of closely related species that can be presumptively identified using commercially available nucleic acid probe tests. Actual speciation, however, would generally require sequencing of 2 to 3 genes (often 16S rRNA, *rpoB*, and/or heat shock protein, or sometimes even whole-genome sequencing as we conducted with isolates 1 and 2 [28]). Because localization of isolate 3 within the *M. avium-intracellulare* complex was sufficient to determine that the isolate was unrelated to the prior 2, we did not pursue complete speciation.

Mycobacterium terrae complex consists of several species of nonpigmented, slow-growing NTM that are only rarely implicated as pathogens. Because the organisms within the *M. terrae* complex are indistinguishable by traditional phenotypic or

mycolic acid analysis methods, the clade has only recently expanded with the widespread use of sequencing. *Mycobacterium arupense* and *M. heraklionense* are the 2 most frequently described species from clinical isolates, though *Mycobacterium virginiense* has been recently proposed as an additional cause of tenosynovitis [8]. Among the rare cases of reported infection, *M. terrae* complex is well described in association with tenosynovitis and osteomyelitis, typically of the hands or fingers [8].

Mycobacterium avium-intracellulare complex consists of 12 species, including *M. avium* and *M. intracellulare*, of nonpigmented, slow-growing NTM [28]. While more commonly implicated in pulmonary disease, lymphadenitis, or disseminated disease (particularly in immunocompromised hosts), *M. avium-intracellulare* complex is also well reported as a cause of skin and soft tissue infection, including tenosynovitis of the hand or wrist [6, 7].

Table 1 summarizes salient clinical features of the reported cases of *M. terrae* and *M. avium-intracellulare* complex tenosynovitis, specifically focusing on more literature since accurate speciation has become possible with widespread use of sequencing, including 2 of the 3 cases reported here. In some case series, nearly 60% of infections were associated with antecedent

trauma, suggesting likely inoculation through broken skin [29]. Concomitant immunosuppression was frequently encountered, although many of the patients with this entity were immune competent. Many patients also received empiric trials of corticosteroid injections prior to their eventual diagnosis with NTM tenosynovitis. Diagnostic delays of months or even years are common, with characteristic MRI findings (eg, rice bodies) or histopathology findings (granulomatous inflammation) offering initial clues. Confirmation of the diagnosis hinges on adequate tissue culture for acid-fast bacilli. Treatment generally requires a combination of surgical debridement followed by directed therapy. While no randomized, controlled trials exist to guide therapy, the majority of observational studies or case descriptions report success with 3-drug combinations that typically include a macrolide, rifampin, and ethambutol. Reported treatment durations range from 2 to 18 months, with the majority being treated for 6 to 12 months.

Upon discovering 3 cases of NTM tenosynovitis with a common epidemiologic link, we had expected the 3 isolates to be the same species and perhaps even exhibit close genetic relatedness. Consistent with prior reports of suspected inoculation through broken skin, we presumed all 3 cases might have been contracted by wood splinters or cutaneous injury to the hands during their shared relief efforts in water-damaged homes of North Carolina. Surprisingly, the isolates belonged to distinct species within *M. terrae* and *M. avium* complexes. The mode of acquisition remained of interest, however, since many NTM occur naturally in association with water and soil. *Mycobacterium avium* complex is easily isolated from household plumbing, municipal water, and soil, even as an intracellular parasite of free-living protozoa [30]. *Mycobacterium terrae* complex has been isolated from the forest environment, water systems, and moisture-damaged buildings, all of which are particularly relevant to the shared epidemiologic exposure of conducting home repair following hurricane damage [31–33]. In retrospect, finding 3 unrelated species seems fitting given that infection with relatively low-virulence organisms that are highly prevalent within the environment depends more on the exposure/inoculation event and host susceptibility than strain-specific traits. In this context, infection would not be expected to behave like more traditional point-source outbreaks (eg, foodborne outbreaks of salmonellosis, *Escherichia coli* 0157:H7).

The term “pseudo-outbreak” or “pseudo-cluster” is sometimes applied to scenarios in which the same organism is isolated from multiple patients but in which subsequent investigation confirms no epidemiologic link [34]. In our evaluation, the opposite occurred: 3 patients developed infection with distinct organisms, despite a shared exposure. Polymicrobial outbreaks have been described in the context of environmental perturbations such as Hurricane Sandy (multiple fungi in burn patients) [35] and Typhoon Morakot (increased seroconversion for *Entamoeba histolytica* and rubella), environmental

contamination after surgery [36], contaminated total parenteral nutrition [37], and related to shared practices associated with central venous catheters [38]. While pseudo-outbreaks often consume a great deal of investigative resources to no avail, case clusters like the one presented here are more likely to be neglected or unrecognized, particularly if diagnosis is significantly delayed after exposure. Such clusters are probably more common than recognized given that exposure to a common environmental source connotes potential for infection with any of the myriad of organisms present in that environment. In this instance, only the unique combination of rare organisms and the patients’ own recollection of a shared exposure triggered recognition of the underlying epidemiologic link.

The inherent difficulties in detecting clusters of infection from a shared source despite being caused by distinct organisms hinders efforts at tracking and preventing such events. Furthermore, the use of sequencing technology, particularly using multiple genes or whole-genome analysis, has enabled clinicians and microbiologists to distinguish organisms that would not previously have been distinguished and recognize novel organisms [39]. This technology presents exciting possibilities to better understand outbreaks of many infections but also presents challenges to standard laboratory-based surveillance, which typically relies on detecting an excess number of isolations of a single microbial species. Novel approaches, such as artificial intelligence systems linked to clinical and laboratory data [40], are needed to address these challenges.

Notes

Author contributions. Conceptualization: J. E. S. and N. A. T.; data curation: N. A. T. and M. I. S.; formal analysis: M. I. S., A. M. X., and D. M. T.; writing, reviewing, and editing: all authors.

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