The World's First and Only Safe and Effective Allergy Vaccine for Poison Ivy (PI) & Poison Oak (PO): Scientific Proposal

(updated 9/14/24)

Wanted: Investors, entrepreneurs, and developers to help commercialize the world's first and only allergy vaccine to safely induce tolerance to PI and (we expect) highly cross-reactive PO

CAPSULE SUMMARY OF VACCINE DEVELOPMENT

We took a set of shortcuts from the methods by which previous PO & PI allergy vaccines had been made, to let us make a small quantity of a home-made vaccine for a single highly allergic patient. These shortcuts led to the world's first successful induction of durable, measurable and clinically relevant real world immunological tolerance to the urushiols of PI &/or PO in a previously sensitized individual.

The Food Drug and Cosmetic act allows an individual physician to make allergy vaccines for his own patients without regulatory oversight, which let us offer the vaccine to others and to modify our dose and formulation based on accumulating experience. Our most effective doses and formulations were 90% effective, 100% of patients with an unsatisfactory initial response responded to a single booster dose, and we had no serious adverse effects.

If we put a price tag on our professional time our hand-made vaccines cost thousands of dollars per course of treatment. To make our vaccine commercially successful we developed a commercial scale production technology to make the vaccine at a cost per initial course of treatment or annual booster of approx. $30-$60, which our economic analysis suggests that we can maximize income by selling at a wholesale price of approx. $300, to treat the tens of millions of Americans expected to want the vaccine as soon as it's validated and available.

A NATIONAL NEED FOR AN EFFECTIVE VACCINE FOR PI/PO

Poison ivy (PI), found east of the Continental Divide, and its highly cross-reactive cousin, poison oak (PO), found west of the Divide, are the most common causes of allergic contact dermatitis in the United States (US). Half of Americans will develop a rash from casual environmental contact at some point and 80-90% will become clinically sensitized with higher levels of exposure (1).

In a 2006 general review of Toxicodendron dermatitis (2), Gladman points out that even 20% of Americans living in urban environments experience clinical allergic contact dermatitis from PI/PO, that allergy to PI/PO causes 10% of all U.S. Forest Service lost-time injuries, and that approximately one third of forestry workers in California, Oregon, and Washington are disabled by poison oak dermatitis each season. During severe fire seasons in the Western United States, up to 25% of U.S. Forest Service firefighters must be removed from duty because of this condition (3). In the late 1990s the cost of treating occupational allergic contact dermatitis from PI/PO consumed 1% of the State of California's entire yearly workers' compensation budget (4).

Other allergy vaccines were marketed for PI and PO prior to 1994, when the FDA began to require proof of efficacy as well as proof of safety and no manufacturer of a previously licensed vaccine submitted efficacy data. Reviewers in 2016 (5) and again in 2019 (6) stressed the need for a better allergy vaccine.

WHY & HOW WE PLAN TO ACHIEVE LOT-TO-LOT VACCINE CONSISTENCY AND GMP COMPLIANCE

The allergens in PI and PO are chemicals called urushiols, molecule side chains of 15 carbon atoms in PI and 17 carbon atoms in PO. Each is found in nature in four different forms, with zero, one, two or three double bonds (another term for unsaturated bonds) near the tail of those carbon side chains. The relative fractions of the different congeners produced by each individual plant is genetically determined. Because of suggestions in the medical literature that different congeners differ in their antigenicity the FDA will require lot-to-lot and year-to-year consistency in both total urushiol content and congener distribution.

We will populate our cultivation greenhouse with clones of plants selected for homogeneity of their genetically determined congener distribution patterns This will build the lot-to-lot and year-to-year consistency required by both medical and regulatory standards into the crop from which we make our vaccine.

We will standardize a concentration protocol to concentrate ethanol extracts of dried leaves to slightly greater than our target concentration of 100 mg / ml and send an aliquot to Cathy in CA for assay to both measure content and confirm congener distribution. Her assay will tell us exactly by what fraction each production lot must then be diluted to precisely yield our target concentration of 100 mg / ml. Bulk vaccine at our target concentration of 100 mg / ml can then be shipped to team member Millan Bhatt's Molecular Pharma Group FDA 503b compounding pharmacy in New Providence, NJ, in production lots dependably below the volume threshold that triggers Hazmat requirements for transportation of volatile flammable solvents. While ethanol is self-sterilizing in practical terms it is not compatible with the FDA test protocols for terminal sterilization so it will be filter-sterilized and aseptically packaged in Millan's facility.

A SAFE & EFFECTIVE VACCINE WITH AN FDA-APPROVED PATHWAY TO BIOLOGICS LICENSURE

I'd been impressed that while the older PI vaccines generally failed to induce total tolerance they often allowed severely allergic patients with unavoidable chronic or recurrent exposures to significantly reduce their need for drugs of the cortisone family. Chronic or repeated treatment with these drugs exposes a patient to a broad spectrum of major side effects. For these reasons and in collaboration with Prof. Catherine Yang, then chair of chemistry and biochemistry at nearby Rowan University, I offered to make a vaccine from locally growing PI for a severely allergic occupationally exposed patient.

We developed a quantitative version of a previously standardized patch test, to measure pre-treatment sensitivity and response to treatment (Tx). We took two shortcuts from previous production methods to make it easier to make small volumes of vaccine in an ordinary chemistry laboratory. We were pleasantly surprised to find that these shortcuts, which we subsequently patented, gave us the world's first and to this date only safe and effective allergy vaccine for the most common cause of allergic contact dermatitis in North America (4).

We'd discovered Vaccine Delivery by Precipitation (VDBP) by injecting a water-insoluble vaccine dissolved in small volumes of ethanol into skeletal muscle, a tissue containing large amounts of available water in which the injected ethanol is rapidly diluted. As the ethanol vaccine vehicle is diluted, the urushiol it carries becomes insoluble and precipitates. The more rapidly the ethanol is diluted, the larger the number and smaller the size of the resulting urushiol particles. We serendipitously hit a sweet spot, depositing hundreds of thousands of particles in the size range of 0.5 to 5 microns within which particles are very efficiently taken up by the naive dendritic antigen-presenting cells that continuously patrol all tissues of the body outside of the blood-brain barrier, and bring those particles of allergen to local and regional lymph nodes in which switching of immune system response takes place.

With informed consent we offered the same treatment to other allergic patients for whom avoidance was either impossible or impractical. The most sensitive two of our first four patients achieved tolerance with our initial formulation and dosing schedule. We modified both formulation and treatment dose on the

basis of accumulating experience, achieving a 90% response rate with our most effective formulations and doses.

A small number of patients with suboptimal responses to all treatment doses requested retreatment, and 100% of these achieved tolerance with a single booster of our most effective formulation and dose. We found no correlation between pre-Tx patch test sensitivity and either disease severity or response to Tx. However, there was a 100% correlation between a 10-fold or greater post-Tx decrease in patch test reactivity and a durable clinical response to Tx (7). This contrasted with a no-greater-than 2-fold variation in patch test response in either absence of Tx or failure of Tx.

We are not eligible for NIH SBIR pre-clinical funding because our chemistry team member, Prof. Catherine Yang, is now employed by a for-profit institution and her share of project work, setting up and performing urushiol assays, would exceed the SBIR program limit for % of grant-funded work that can be performed by a for-profit collaborating entity that isn't itself a small business. We are therefore seeking VC &/or private investor funding to bring the vaccine through the regulatory process and to set up and validate the production strategy we designed for precise, cost-effective commercial scale vaccine manufacture.

PRE-CLINICAL R&D

Use of concentrated but unpurified crude ethanol leaf extract as our clinical trial and commercial vaccines:

A highly purified urushiol vaccine was less effective than the same vaccine when mixed with a small amount of crude, unpurified ethanol leaf extract. This tells us that an unidentified substance or combination of substances present in crude, unpurified extracts is important for optimal efficacy. The lack of significant adverse reactions to any of the vaccines we studied in our human proof-of-concept experience suggests that our decision to commercialize an unpurified formulation with superior efficacy does not carry a downside risk of increased adverse effects. Our vaccine will join the large majority of FDA-approved allergenic products made from natural source materials in neither having nor needing a listing of ingredients other than its active pharmaceutical ingredients (the 4 congeners if urushiol) and added substances also present in the formulation (ethanol). Our decision to use an unpurified concentrate as a vaccine will also reduce costs of manufacture.

This summer (2024) hydroponic vegetable farmer team member Merlin Weaver is testing standard agricultural cloning methods, to have a protocol available to populate our cultivation greenhouse when we have the funding to set up both the greenhouse and the urushiol assay. He is also monitoring plants with and without supplemental LED lighting to see if maintenance of a 16 hr illumination cycle will prevent the plants from going into their normal end-of-summer dormancy an give us an extended growing season.

Round 1 funding will also allow Prof. Yang to set up her cost-efficient wt/wt urushiol assay, to be ready for the shelf life stability study, to identify vines with identical or near-identical congener distribution patterns for cloning to populate our cultivation greenhouse, and to monitor the preparation of vaccine from ethanol extracts of oven-dried leaves.

Selection and validation of vaccine production technology

The FDA requires that any pharmaceutical or biological product approved for commercial sale be functionally identical to the version of the same product used in its pivotal clinical trials. For a completely chemically defined pharmaceutical product pilot lot production of clinical trial product can be outsourced and produced by other than the proposed exact commercial scale technology as long as physical and chemical identity of the resulting products can be confirmed. This cannot be done for a biological product derived from natural source materials that is not completely chemically defined. Clinical trial lots of a vaccine such as ours must therefore be produced by methods that are physically or functionally identical to the methods proposed for commercial scale manufacture. Functional identity will let us use scaled down versions of each step of proposed commercial scale production as long as each scaled

down step can be confirmed to do exactly the same thing in the sequence of steps proposed for commercial vaccine production. His means cultivation of the same mix of genetically selected plants under the same conditions of cultivation, treatment and extraction of leaves in the same manner, conversion of extract to vaccine in the same manner and functionally identical packaging of the vaccine for compliance assays and use.

As soon we have all of Round 1 funding, time to set up and equip the cultivation greenhouse ****** and he modular building to house extract concentration and pour a concrete floor and equip the smaller greenhouse we plan to repurpose for and it's a time of year at which naturally growing source plants are available we will begin the two operations needed to prepare for clinical trials. The first is a comparative shelf life stability study to select optimal conditions for vaccine packaging and storage. The second is the selection, cloning and cultivation of plants with sufficiently uniform congener distribution patterns to build the lot-to-lot consistency required to meet both medical and regulatory requirements into our crop, and to produce enough GMP vaccine from their leaves for clinical trials. Each of the two projects will require repeated quantitative assays for urushiol content and congener distribution, for which chemistry team member Catherine Yang will set up her cost-effective wt/wt urushiol assay in CA.

We will perform shelf-life stability studies with vaccine made from naturally growing leaves harvested from the same field we used in the past. Our goal will be to minimize the degree of water contamination of the final product as even trace amounts of water can expedite urushiol degradation. Rigorously desiccated urushiol and urushiol vaccines appear to retain full or nearly full activity almost indefinitely, even in sunlight and at room temperature (8).

Our preparation protocol for the vaccine we plan to bring to each of shelf-life stability study, clinical trial and commercial sale is as follows:

1. **"Oven-dry" freshly harvested leaves at 50 deg C in a circulating microbiological incubator to remove their 2/3 by wt natural water content.** Drying of fresh leaves will be performed in a leased, otherwise unused small greenhouse in which we will pour a concrete slab floor with slopes and depressed gutters designed for easy hose cleaning.
2.
    a. Shelf-life stability studies will be performed with naturally grown leaves, pooled without regard to genotype and congener distribution, to be harvested from the same field that was the leaf source for our human proof-of-concept vaccines,

    b. Clinical trial and subsequent commercial sale vaccines will be made from hydroponically greenhouse-grown cloned nodes of naturally growing vines from the same field, selected for identify or near-identity of their genetically determined urushiol distribution pattern to build the lot-to-lot and year-to-year consistency required for regulatory approval into our leaf source.

3. **Extract the leaves with pharmaceutical grade 100% ethanol at a ratio of 9 ml ethanol per gram of dried leaves. F**or shelf life stability study and clinical trial pilot lot production extraction will be performed in ½ gallon home canning jars filled except for a small air bubble to facilitate mixing on inversion twice daily for 7 days, after which the now dark green ethanol is decanted and filtered to remove leaf and stem residue.
4.
    a. We expect the urushiol concentration of the resulting crude ethanol extract to be in the range of 3-4 mg/ml for naturally growing leaves, though we hope to achieve 2-3x that concentration with leaves cultivated under controlled growing conditions.

    b. Ethanol extraction will probably be performed in the small greenhouse in which we want to pour a concrete floor and use for leaf crying. Vacuum concentration will be performed in a modular building to be set up in close proximity to the cultivation and drying greenhouses. The modular building will require plumbing, septic system drainage and a shower to wash if or when needed after accidental contact.

5. **Concentrate the crude ethanol extract by solvent evaporation under vacuum to a concentration slightly > 100 mg / ml, to permit assay and then dilution of each lot to our exact target concentration of 100 mg / ml.**

6. **Ship vaccine concentrate to packaging team member Millan Bhatt at his Molecular Pharma Group location in New Providence NJ for non-GMP packaging to compare shelf-life stability under the following conditions:**

    a. Liquid phase packaging in injection vials under reasonably achievable desiccating conditions and in a dry nitrogen environment.

    b. Packaging after solvent evaporation under vacuum in a lyophilization process. The reason for including this process as a packaging option is that desiccated ethanol will itself act as a desiccant and pull any available water molecules out of is microenvironment to dilute itself toward its azeotropic concentration of 95.63% ethanol and 4.37% water. As even trace amounts of water facilitate the degradation of urushiol we want to see whether the added costs of putting the vaccine through a lyophilization process and the cost and user inconvenience of providing GMP ethanol for reconstitution and requiring its use before vaccine administration provide a sufficient improvement in shelf life stability to justify their use.

        i. This will not be true lyophilization (freeze-drying) as ethanol remains liquid at lyophilizer temperatures.

        ii. The resulting product will not be the dry powder produced by true freeze-drying but the same viscous (thick) oil produced by vacuum evaporation of ethanol at room temperature. Redissolution after solvent evaporation is theoretically a potential problem but the oil resulting from vacuum evaporation of urushiol solutions in ethanol was confirmed to redissolve readily and completely upon reconstitution (8).

    c. We can calculate the volume of ethanol needed to reconstitute each vial to its exact target urushiol concentration of 100 mg / ml by weighing an uncapped vial before and after solvent evaporation. We can confirm the accuracy of our calculation and make any necessary adjustments by measuring urushiol content after reconstitution. This “pseudolyophilization” step will add to packaging costs but may be justified if it yields a sufficient increase in shelf-life stability to justify its costs

    d. Shelf-life stability will be compared under storage at both 5 and 25 deg C. Without the phase change of freezing of the vaccine we would not anticipate any added benefit from storage below the freezing point of water. Demonstration of shelf-life stability at 25 deg C will justify asking the FDA to allow unrefrigerated vaccine storage.

    e. We will study the effect, if any, of 2 weeks at either 40 or 50 deg C on subsequent shelf-life stability at 5 and 25 deg C. If we have achieved sufficient desiccation to tolerate these exposures to heat shock, we’ll be able to ask the FDA to allow unrefrigerated shipping during part or all of the year to some or all U.S. zip codes.

        i. The ability of urushiol in situ in intact leaves and stems to tolerate drying for 72 hrs at 50 deg C does not guarantee tolerance of exposure to the same temperature when dissolved in ethanol. Urushiol’s physical/chemical microenvironment where it naturally exists in leaves and stems may be stabilizing in ways not replicated in ethanol solution. We expect to achieve the greatest

shelf life stability by aggressive desiccation and secondarily by exclusion of oxygen (sealing of vials under dry nitrogen.

In our 2020 pre-IND meeting, the FDA approved a no-obstacles pathway to regulatory approval based on our human proof-of-concept experience. Their only requirements are that we:

1. standardize methods for vaccine production and packaging,
2. propose target levels and (for their approval) tolerance limits for total urushiol content and congener distribution, and
3. make all vaccines intended for human use in compliance with Good Manufacturing Practices (GMP).

As noted above, we will build compliance with the lot-to-lot consistency requirement into our plant source by only populating our greenhouse with clones of plants whose genetically determined congener distribution patterns are identical or nearly identical. While ethanol is functionally self-sterilizing it is not compatible with FDA requirements to claim terminal sterilization, as a result of which the vaccine must meet requirements for aseptic packaging. We will accomplish this by filter-sterilizing the vaccine as It is passed into Millan's clean room for vial filling, pseudolyophilization of elected lots, and sealing in a dry nitrogen environment.

Our fastest pathway to the marketplace will be to make vaccine from the same leaf source we've already proven to be safe and effective for PI. This field is atypical in that the owner of the property, on which her home is located, has never seen a blossom or berry in the 30+ years she's lived there. This suggests that her field is populated entirely or almost entirely by male plants which by themselves can only propagate by asexual reproduction.

As a result, we expect this field to have large numbers of vines suitable for cloning that have identical genetically determined congener distribution patterns. This will let us very quickly populate our 2880 sq. ft. cultivation greenhouse with more as many plans as it will accommodate, with identical or near identical urushiol congener distribution patterns.

With optimization of supplemental LED lighting, nutrition and environmental conditions according to known agricultural principles for proliferation of leafy green plants, we see a reasonable likelihood of being able to produce enough crop in a single growing season to begin clinical trials without further delay. Production for completion of clinical trials, if more vaccine is needed, and for initial commercial sale, will be ongoing.

CLINICAL TRIALS

Choosing clinical trial treatment schedules for maximum marketability: The efficacy of our vaccine is a function of cumulative treatment dose. The frequency and severity of adverse effects, almost exclusively injection site reactions with a rare case of transient urticaria with eosinophilia, depends on starting dose, number of steps and dosage increments in the treatment schedule. We presently plan to compare treatment doses of 15, 25 and 35 mg in Phase 1 dose-ranging clinical trials. Our human proof-of-concept experience suggests that schedules of 6 steps for cumulative treatment doses of 15 mg of urushiol, 7 steps for cumulative doses of 25 mg and 8 steps for combative doses of 35 mg, should yield adverse event profiles sufficiently benign for the FDA to allow administration in retail pharmacies and other setting without direct physician supervision.

We plan to offer a dose-tracking database to make it easy for patients to get accurate sequential doses anywhere in North America. If a complete cumulative target treatment dose has not been received within a consecutive 4-month period, the program can recommend an additional dose to make up any deficiency.

Validation of primary endpoint and no need for placebo control arms: Allergic members of the FDA team that conducted our 2020 pre-IND meeting suggested a clinical trial design that will

simultaneously validate our proposed primary endpoint (a 10-fold or greater reduction in sensitivity by our quantitative patch test) and eliminate our need for placebo control clinical trial arms. Their suggestion was that we patch test every study subject twice before treatment and a third time after treatment. The difference in sensitivity between the two patch tests results without treatment, which in our human proof-of-concept experience has never been more than 2-fold, will serve each patient's personal placebo control against which to measure his or her reduction in sensitivity after treatment, for which a 10-fold or greater loss has had a 100% correlation with the induction of clinical tolerance.

Booster doses: We know from our human proof-of-concept experience that tolerance is lost at different times post treatment in different individuals. We know from limited experience that patients who have totally lost tolerance respond to retreatment, but that they again require multi-step dosing to control their risk of injection-site reactions. We know that patients with less-than-satisfactory responses to initial treatment respond to one-step booster doses without adverse reactions. We have not seen any human proof-of-concept responders to our most effective cumulative treatment doses of 16 to 23 mg totally lose tolerance in less than 11-13 months, though a minority of patients may lose tolerance by 2 years.

Maintaining approval for administration in retail pharmacies will depend on not having significant numbers of reactions that either a physician or a patient might perceive as needing medical care. require physician care. We will therefore perform booster safety/efficacy studies 13 months after completing initial treatment as a basis to request FDA approval to recommend and offer booster doses at 11–13-month intervals. We will plan a small (10-12 subject) safety study of one-step booster doses 13 months after completion of initial treatment in early clinical trial responders. Their adverse events profile will determine whether we perform 13-month pivotal booster safety/efficacy trials with one step or 2-step dosing schedulers. The dose-tracking database will be configured to notify patients at 10, 11 and 12 months that it's time for their boosters. It will route patients who have not received boosters 11-13 months after their most recent previous dose to repeat the initial vaccine sequence.

Organization and conduct of clinical trials: A biopharmaceutical VC company that invests in companies for which it becomes the manager of their clinical trials has expressed interest in becoming our clinical trial management company. Our clinical trial needs are sufficiently different from the drug trials that are the bread and butter of most contract clinical research organizations that a sampling of contract CROs whose names came up in a Google search for CROs that accept studies involving vaccines were uniformly uninterested in our clinical trial needs. Alternatively, interested allergists who already conduct contract clinical research in their practices or who might specifically be interested in participating in clinical trials of this vaccine, could be recruited through the two allergy specialty societies of which Dr. Coifman is both a fellow and a past scientific committee chair. We are confident that if needed we can put together a clinical trial network for this project and find a qualified lead investigator who would not have the conflict of interest of having an ownership interest in a positive outcome

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Team consultant member Scott Oneto independently works with large employers with workforces occupationally exposed to PO. He advised us that some of these employers or consortia of these employers may want to sponsor and fund clinical trials for their exposed and allergic employees. These will be options if approved by both the FDA and the IRB.

Currently proposed clinical trials:

Phase 1: 10 subjects treated with cumulative doses of 15, 25 and 35 mg of urushiol. A decision for which dose to bring to clinical trial will depend on not just safety and efficacy counts but also the extent by which the different doses reduce patch test reactivity. In our human proof-of-concept experience, successful inductions of tolerance were associated with 10-fold to 5000-fold reductions in sensitivity. There was a general correlation between the factor by which sensitivity was reduced and the duration of that patient's tolerance. Unless the FDA requires otherwise, we will only perform a Phase 1 dose ranging study in a study center east of the Continental Divide, where subjects will be exposed and allergic to PI but not PO.

Phase 2: Subject to biostatistician recommendation to test different numbers of subjects, we will test and treat 30 subjects at one or split between two centers located east of the Continental Divide, exposed and allergic to PI, and an equal number at one or two centers in the drier climate of the West, where the plant to which subjects will be exposed and allergic is PO.

If the FDA allows, we'd like to offer a single booster dose to any clinical trial subject who fails to achieve our primary endpoint of a 10-fold or greater reduction in patch test sensitivity following initial treatment. All clinical trial subjects will be asked to report any recurrence of symptoms in a 1-10 severity scale setting their personal pre-treatment severity as level 10. Responders will be asked to return for follow-up patch testing 12-13 months following completion of initial treatment, at which time they may also be offered boosters.

Trials of annual booster safety and efficacy: Depending on subject numbers requested by the FDA, we will invite a subset or all study subjects returning for 12-month follow-up patch tests to participate in a clinical trial of boosters. The current plan is to begin with boosters containing a complete cumulative initial treatment dose in a single step. If one-step boosters turn out to elicit significant injection site reactions, we will default to a two-step booster schedule.

We will want to repeat patch testing 2-4 weeks after completing booster treatment with the same requests for quarterly symptom reports and to return for another set of patch tests 12-13 months after receipt of first annual booster. We may want to offer a second annual booster as an incentive to subjects to return for one-year post first annual booster patch tests.

Additional (limited) clinical trials to extend vaccine use life: Initial clinical trials will of necessity be performed with relatively new lots of vaccine. Urushiol is not the only active ingredient of our vaccines. We confirmed that something present in crude ethanol extracts contributes to vaccine efficacy but is lost in urushiol purification, as a highly purified urushiol was less effective than the same amount of unpurified urushiol and mixing the purified urushiol with additional crude extract restored its efficacy to that of a completely unpurified vaccine. We don't know what this substance is, which is not a problem under FDA regulations for allergenic products derived from natural source materials, but without being able to directly measure its own shelf life stability he only way we can validate extensions of vaccine use life is by clinical trial. We will negotiate with the FDA for what we hope will be small and inexpensive trials of increasingly older lots of vaccine.

Cross-efficacy of PI vaccine for PO highly likely but not 100%:

The urushiols of PI and PO are sufficiently cross-reactive that an effective vaccine for PI is likely to be equally effective for PO. Until it's confirmed in clinical trials, however, it cannot be guaranteed. In the unlikely event that our vaccine meets efficacy criteria for PI rot not for PO our plan would be to license it for PI alone, which is the source of the urushiol to which 80% of the U. S. population is exposed.

Income from sales for PI would more than cover costs to make a similar vaccine from PO to be cultivated under similar conditions. We can then make and validate a combination vaccine containing both PI and PO.

We thank you for your interest in this product and this project.

Robert E. Coifman, M.D.

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