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

(updated 3/4/25)

Wanted: Investors to help commercialize the world's first and only immunotherapy antigen (allergy shot) proven in human patients to safely induce durable, measurable, real world immunological tolerance to PI and (we expect) highly cross-reactive PO

NOMENCLATURE: Antigenic products administered to induce tolerance were called allergy vaccines until the name, Vaccine, became divisive. To not alienate potential recipients because of negative associations with the word "vaccine" we will call them what vaccines are, "antigenic products administered for immunotherapy," "immunotherapy antigens," or, colloquially, "allergy shots."

CAPSULE SUMMARY OF FORMULATION DEVELOPMENT

The Food Drug and Cosmetic act allows physicians to make allergenic products from natural source materials for their own patients without regulatory oversight. This let us make our own allergy shots for a single highly allergic and occupationally exposed patient. To make it practical to make a small lot of treatment antigen without a closed sterile formulation facility we took a set of shortcuts from previous formulations. These unexpectedly resulted in Antigen Delivery by Precipitation (ADBP), a new and potent way to deliver antigens to the immune system. Instead of the partial relief we expected, our patient surprised us with the world's first successful induction of complete immunological tolerance in a previously sensitized human. We developed a patch test to measure sensitivity, offered the same treatment to others, and achieved tolerance in the most sensitive two of our first four patients. With dose and formulation changes guided by accumulating experience we achieved a 90% response to initial treatment with a 100% response of those with an unsatisfactory initial response to a single booster dose. We had no significant adverse effects..

How ADBP works: Urushiol is soluble in ethanol but insoluble in water. Our immunotherapy antigen is a concentrated, unpurified ethanol extract of oven-dried leaves. Concentration allows effective treatment doses to be given in small volumes of ethanol to minimize tissue irritation and discomfort. Unpurified extracts are not only less expensive than purified urushiol solutions, but also more effective and are permitted by FDA regulations for allergenic products derived from natural source materials.

Previous urushiol immunotherapy antigens were also unpurified extracts but dissolved in sterile vegetable oils and injected under the skin. The urushiol remained in the injected blobs of oil, and diffused into the surrounding tissue fluid one molecule at a time. In ADBP, the urushiol is dissolved in ethanol which mixes freely with tissue fluid by which it is rapidly diluted following injection. As the ethanol in which it's dissolved is diluted by the water content of the muscle into which it's injected, the urushiol becomes insoluble and precipitates. The faster the dilution, the larger the number and smaller the size of the resulting particles. Our shots worked where others had failed because we happened to achieve a dilution rate that deposited hundreds or thousands to millions of urushiol particles in the 0.5 to 5 micron size range that are bite-sized snack food for the wandering dendritic antigen-presenting cells that patrol all body tissues outside of the blood-brain barrier, looking for interesting antigens to bring to draining lymph nodes for processing (1).

A NATIONAL NEED FOR AN EFFECTIVE TREATMENT FOR ALLERGY TO PI/PO

Poison ivy (PI), which predominates east of the Continental Divide, and its highly cross-reactive cousin, poison oak (PO), which predominates in the drier climate of the West, are the most common causes of allergic contact dermatitis in the United States (US). Eighty-five % of Americans will become sensitized with sufficient exposure and half of Americans will seek medical care for these allergies at some point in their lives (2).

In a 2006 general review of Toxicodendron dermatitis (3), 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 (4). 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 (5).

Informal surveys suggest that 3-5% of the U. S. population, or 6-10% of the 185M Americans who will seek medical care for these allergies at some point, have sufficiently chronic or frequently recurring disease from exposures they either cannot avoid or find it impractical to avoid to want a safe, effective, convenient and affordable treatment as soon as one becomes available.

Other allergy shots were marketed for PI and PO until 1994, when amendments to the Food Drug and Cosmetic act first required proof of efficacy as well as safety for allergenic products derived from natural source materials and no manufacturer of a previously licensed product submitted efficacy data. Authors of review articles in 2016 (6) and again in 2019 (7) and 2024 (8) stressed the need for a more effective way to induce tolerance to these antigens. ***We submit that our technology satisfies this need.***

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

The allergens in PI and PO are chemicals called urushiols, molecules consisting of a common ring structure with side chains of 15 carbon atoms in PI and 17 carbon atoms in PO. Each is found in nature in four different forms, called congeners, with zero, one, two or three double bonds (another term for unsaturated bonds) near the tail of those carbon side chains. The ratios 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, both the FDA and principles of scientific integrity 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 immunotherapy antigen.

We will dry freshly harvested leaves to remove their 2/3 by wt content of water, which if left in place complicates antigen production and facilitates urushiol biodegradation (9). Urushiol will be extracted from dried leaves with ethanol and the resulting crude ethanol extract concentrated to a urushiol content slightly greater than the 100 mg / ml at which strength it will be used for treatment. Not only is concentrated crude ethanol extract less expensive to produce than purified urushiol at the same concentration, but the unpurified antigen is also more effective. It contains an unidentified substance that contributes to effectiveness but is lost in the process of purification. Unidentified substances are present in all or nearly all FDA-approved allergenic products derived from natural source materials, and are not a regulatory problem as long as production methods are standardized to make the lot-to-lot content of unidentified ingredients as reproducible as possible.

We will ship urushiol concentrate to team member Millan Bhatt's Molecular Pharma Group FDA 503b compounding pharmacy in New Providence, NJ, where it will be assayed and diluted to exactly 100

mg/ml, filter-sterilized (as ethanol does not satisfy the FDA's requirements for terminal sterilization), and aseptically packaged in multi-dose injection vials under desiccating conditions.

SAFE & EFFECTIVE ALLERGY SHOTS WITH AN FDA-APPROVED PATHWAY TO BIOLOGICS LICENSURE

We followed our first successful induction of tolerance by offering the same treatment to others. 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 to initial treatment with our most effective formulations and doses.

A small number of patients with suboptimal responses to initial treatment accepted our offer of a booster dose, which achieved durable and measurable real world tolerance in 100%. While response to the low cumulative treatment doses given to our first four patients was strongly correlated pre-treatment (Tx) patch test sensitivity we observed no such correlation with the 20-fold higher doses we subsequently found to be 90-100 effective. We also found no correlation between pre-Tx patch test sensitivity and reported clinical severity. 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 (10). This contrasted with a no-greater-than 2-fold variation in patch test response in either absence of Tx or lack of clinical response.

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 Round 1 private investor funding to validate the production strategy we designed for precise, cost-effective commercial scale manufacture and make clinical trial treatment antigen.

PRE-CLINICAL R&D

Highly purified allergy shots were less effective than when the same urushiol concentrate was mixed with a small amount of crude, unpurified extract. This told 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 formulations 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 allergy shots will join the large majority of FDA-approved allergenic products made from natural source materials that require direct or indirect assays of known active pharmaceutical ingredients but address standardization of ingredients that cannot be identified by standardization of preparation protocols.

In 2024 hydroponic vegetable farmer team member Merlin Weaver validated the cloning protocol with which he will populate our cultivation greenhouse with plants with identical or near-identical genetically determined urushiol distribution patterns, to build the required lot-to-lot consistency of our end product into the crop from which it will be made. He also confirmed that supplemental LED lighting keeps the plants from entering dormancy as days become shorter, giving us a 12-month greenhouse growing season.

Round 1 funding will allow Prof. Yang to set up her low-cost urushiol assay, for which we are preparing an application for patent protection. Her assay is semi-quantitative rather than quantitative but sufficiently precise and reproducible to meet regulatory standards as a measure of lot-to-lot consistency. Its advantage compared to a quantitative molecular assay is its cost at commercial scale of $50-75 per assay while the cost of the quantitative molecular assay is ~$800.

When her assay becomes available we will begin shelf life stability studies for antigen made from naturally growing PI under different conditions of storage. We will compare storage at room temperature with storage under refrigeration. If its major congeners are stable at room temperature that data will let us ask the FDA to permit room temperature storage, reducing our cost to provide shots for end users. We will study the effect on immediate congener stability and subsequent shelf life stability of 14 days at each of 40 and 50 deg C before return to either room temperature or refrigeration. If there is no adverse effect of 14 days at 40 deg C we can ask the FDA to let us ship without refrigeration to most US destinations, most of the year. If there is no adverse effect of 14 days at 50 deg C we can request approval to ship without refrigeration to all US destinations at any time of year, again reducing costs. We will track longer term thermally stressed shelf life stability at both 50 and 65 deg C, at which stability will support requests to extend authorized use life at lower storage temperatures beyond what time will have let us actually measure at those temperatures. Published data suggests that the most critical factor for long term urushiol stability is protection from even trace contamination with water (8). We plan to employ handling methods that minimize risks of water-contamination at all steps of processing.

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

1. Standardize methods of production and packaging,
2. Propose target levels and (for their approval) tolerance limits for total urushiol content and congener distribution, and
3. Make all antigen intended for human use in compliance with Good Manufacturing Practices (GMP).

As previously noted we will build compliance with the lot-to-lot consistency requirement into our plant source by only populating our greenhouse with clones of plants for which the genetically determined congener distribution patterns are preselected to be identical or nearly identical. While ethanol is functionally self-sterilizing it does not by itself meet GMP requirements for terminal sterilization. The antigen and any dilution ethanol needed for reconstitution will be passed into Milan's clean room through sterilizing filters before final assay and GMP-compliant packaging.

In the only published characterization of urushiol extracts of dried leaves Spain and Cooke (8) used an extraction ratio of 9 ml anhydrous ethanol per gram of dried leaves. Our own small observational trial suggests that it may be more efficient for us to use a lower extraction ratio. This will reduce costs to both purchase new ethanol and dispose of used ethanol as a flammable hazardous waste. It will also reduce the time needed for vacuum concentration.

CLINICAL TRIALS: The following are our clinical trial plans pending approval by the FDA, which offered to give us a second pre-IND meeting at no cost when we have final specifications for the product we plan to bring to clinical trial.

Choosing clinical trial treatment schedules for maximum marketability: The efficacy of our immunotherapy antigen 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 relative dosage increments between steps of the treatment schedule. We presently plan to compare treatment doses of 14, 23 and 32 mg in Phase 1 dose-ranging clinical trials. Our human proof-of-concept experience suggests that schedules of 5 steps for cumulative treatment doses of 14 mg of urushiol, 6 steps for cumulative doses of 23 mg and 7 steps for combative doses of 32 mg, should yield sufficiently benign adverse event profiles for the FDA to allow administration in retail pharmacies and other similar settings without on-site physician supervision. If these schedules prove too fast, we can reduce the adverse reaction rate with a lower starting dose and an additional step or two to achieve the target cumulative dose.

Validation of primary endpoint and no need for placebo control arms: The senior allergist on the FDA team that conducted our 2020 pre-IND meeting is the same person who pulled the previously licensed PI and PO immunotherapy antigens from the market in 1994 when their sponsors failed to submit data confirming efficacy. He and his team were enthusiastic about the prospect of being able to license safe and effective shots for these allergies and offered us an obstacle-free pathway through the regulatory process. They proposed that we patch test every study subject twice before treatment and a third time after treatment, so that the difference if any between each subject's two pre-treatment patch tests would constitute his or her own placebo control. They recognized our finding of a 100% correlation between a 10-fold or greater loss of patch test sensitivity following treatment and the achievement of clinically relevant immunological tolerance, by agreeing to accept a 10-fold or greater reduction in patch test sensitivity as our primary clinical trial endpoint with 12 month quarterly questionnaires to track maintenance of tolerance as a secondary endpoint. They further agreed to a pivotal clinical trial design that essentially replicates both the treatment antigen and the recipient population with which we achieved 90-100% efficacy with 100% safety in our human proof-of-concept experience.

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 this 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 booster doses without adverse reactions. We did not encounter any loss of tolerance in less than 13 months in human proof-of-concept responders to the doses we want to bring to clinical trial, though some patients lost tolerance by 2 years. We will incentivize clinical trial subjects to return for repeat patch testing 12 months after completion of initial treatment with an offer of a free booster dose in addition to an honorarium

Achieving and maintaining FDA approval for administration in retail pharmacies will depend on not having significant numbers of reactions that either a physician or a reasonable patient might perceive as needing medical care. We will ask the FDA to authorize clinical trials of booster safety and efficacy given 12-13 months after completion of initial treatment, to validate booster dosing at 11–13-month intervals. We will plan a small (10-12 subject) safety study of one-step booster doses 12-13 months after completion of initial treatment in early clinical trial responders. Their adverse events profile will determine whether we perform 12-13-month pivotal booster safety/efficacy trials with one step or 2-step dosing schedulers.

We plan to offer a post-marketing dose-tracking database to make it easy for patients to get accurate sequential doses at any participating retail pharmacy in the U. S. (This will not apply to clinical trial subjects who except under very unusual circumstances must complete their clinical trials at their originally registered centers.) For any patients (not clinical trial subjects) who have not completed the FDA-approved initial treatment schedule within a consecutive 4-month period, we'll request permission from the FDA to write corrective measures short of requiring repetition of the entire treatment schedule into the program based on general principles of allergen immunotherapy, without having to specifically having to validate each individual deviation by clinical trial. The database can be configured to notify patients at 10, 11 and 12 months that it's time to get boosters. Because of inability to determine which patients who miss their 13-month booster dosing interval will need what dose adjustment to prevent injection site reactions that could require treatment without repetition of patch testing, the dose-tracking database will prescribe repetition of the complete initial treatment series for all patients who miss their 13-month booster target. We see rigorous booster schedule enforcement as essential to maintain a sufficiently benign adverse reaction frequency-severity profile for the FDA to continue to allow retail pharmacy administration.

Organization and conduct of clinical trials: We are currently in discussion with the managing partner of an allergy group that runs a large clinical trial program, to become our medical director for clinical trials and recruit study centers in areas in which each of PI and PO is the predominant allergen. We are also talking with a VC company that has its own clinical research organization (CRO) and invests in companies for which it becomes the provider of CRO services. While I don't want to have to take the time to do so, myself, as a member of the Immunotherapy Committee of the American Academy of

Allergy Asthma and Immunology and a past chair of one of its subcommittees I have the contacts to recruit a network of centers from Academy member allergists who conduct sponsored clinical research in their allergy practices.

Team consultant member Scott Oneto independently works with large employers in the western states 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. They will also be early adopters as soon as shorts are approved and validated for allergy to PO.

Currently proposed clinical trial details:

Phase 1: 10 subjects will be treated with cumulative doses of each of 14, 23 and 32 mg of urushiol. A decision for which dose to bring to clinical trial will be based on adverse events profiles, the frequency of achieving our endpoint of a 10-fold or greater reduction in patch test sensitivity and the distribution of pre and post-treatment patch test reactivity scores. (In our human proof-of-concept experience there was no correlation between clinical sensitivity and absolute patch test sensitivity but clinically sensitive patients who were less sensitive by patch testing generally required larger treatment doses to achieve tolerance.)

We will only perform dose-ranging Phase 1 studies in centers east of the Continental Divide, where subjects will be exposed and allergic to PI.

Phase 2: Subject to biostatistician recommendation to test different numbers of subjects, we will test and treat 30 subjects exposed and allergic to PI at one or two centers east of the Continental Divide, where PI is the predominant source of urushiol exposure, and an equal number exposed and allergic to PO at one or two centers where PO predominates, in the drier climate of the West.

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 on a 1-10+ severity scale setting their personal pre-treatment severity as their personal level 10. Responders will be asked to return for follow-up patch testing 11-12 months following completion of initial treatment, at which time they will be offered boosters and invited to participate in a post-booster year of tracking with the added incentive of a voucher for another free booster in a participating retail pharmacy at that time (by which we expect the antigen to be commercially available).

Trials of annual booster safety and efficacy: Depending on subject numbers to be negotiated with 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. Our 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 a significant frequency of 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 a 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 approved use life: Initial clinical trials will of necessity be performed with relatively new lots of antigen. Urushiol is not its only active ingredient

We confirmed that an unidentified substance present in crude ethanol extracts contributes to the efficacy of the antigen but is lost in urushiol purification, as a highly purified urushiol was less effective than the same amount of unpurified urushiol. Mixing purified urushiol with additional crude extract restored its efficacy to that of a completely unpurified formulation. We don't know what this substance is, which is not a problem under FDA regulations for allergenic products derived from natural source materials. With no other way to measure its own use life stability our only way to validate extensions of use life for the

product that uses it 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 antigen.

Extending labeled use life will help rather than hurt sales: Use life stability testing beyond two years is seen as an economic liability in much of the biopharmaceutical industry: Two years will almost always get a product through the supply chain with at least a year of remaining use life when it reaches the buyer, who, if he absolutely needs to have it, will often buy more when remaining stock on hand goes out of date. We not only differ philosophically in wanting to be paid well for a product that is also cost-effective for the buyer, but we also believe that a longer use life will also help sell more product. Our major buyers will be retail pharmacy chains and pharmacies, many in locations in which anticipated demand will be light. The longer the use life we can provide for both unopened and opened multi-dose vials, the larger the number of locations at which potential buyers will calculate that demand for shots will cover their cost of stocking the antigen in potentially low demand locations.

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

The urushiols of PI and PO are sufficiently cross-reactive that allergy shots that work for PI are just as likely to work for PO. Until it's confirmed in clinical trials, however, it cannot be guaranteed. In the unlikely event that our antigen 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 antigen from PO to be cultivated under similar conditions. We could then make and validate a combination product containing concentrated ethanol extracts of both plants.

Post-marketing surveillance:

We can use the same dose-tracking database to invite patient to report both duration and any loss of clinical tolerance and any suboptimal experiences they may encounter in association with treatment. This data will give us guidance toward product improvement over time.

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

Robert E. Coifman, M.D.

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