Precision-Guided Vaccines LLC

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We're a biotech startup company, and we think we've figured out a pathway that will enable vaccine companies to create better vaccines than have ever been available, before now.

That's an extremely bold claim, so we invite any and all experts to approach it skeptically, and see if they can find any flaws in the path we have identified, or in any of the steps we're using to explore and travel down that pathway. If you think you have spotted a flaw . . . or, if you think you might have figured out a better way to do something we're doing . . . or, if you want to contact us, find out more, and possibly consider whether you might want to get involved at an early stage, while things are still wide open – feel free to contact us, via the last page of this website.

Our approach starts with a crucial aspect of how immune systems function, in all vertebrate animals. Immune cells distinguish between "self" particles (which must be tolerated), versus "non-self" invaders (which must be defended against) by using specialized "receptor proteins", which have an exposed portion on the outer surface of the cell, and an internal portion, inside the cell.

The details and mechanisms of how immune cells perform that task, and actually distinguish between "self" versus "invader" (while also figuring out how to tolerate the "good" bacteria that help digest food), are highly complex; however, people don't need to understand those details. Instead, the point that needs to be understood, for now, is simple: immune cells use "receptor proteins" on their surfaces, to distinguish between "non-self" pathogens, versus "self" cells.

So, that led to a first question: would it be possible to create new types of vaccine particles having "transport peptides" attached to their surfaces, which might be able to increase the speed and potency of how those modified vaccine particles are taken in and processed? Or, stated in alternate terms, would it be possible to "trick" and "fool" one or more types of immune cells into "believing" that vaccine particles – if those particles

have “pathogen-signaling peptides” attached to their surfaces – are actually dangerous and important pathogens, which need to be responded to, and defended against, as rapidly as possible?

That initial question led to two follow-up questions:

1. Which immune cells would be the best immune cells to “target”, if we began looking for ways to create vaccine particles that would be recognized rapidly by those “targeted” immune cells, and pulled into those cells, and processed in ways that will form antibodies?

– and –

2. What would be the best way to identify a set of “pathogen-signaling transport peptides” which could “trick and fool” a set of targeted immune cells into “believing” that vaccine particles carrying those “transport peptides” are dangerous and important pathogens?

The best answers we’ve been able to come up with so far – and, this is where we challenge any experts to see if they can come up with any better answers (and, any experts are not just allowed, but encouraged, to use any AI system they know how to use, to help them analyze what we are doing) – can be summarized as listed below.

Each header (in red, below) is a link; if you click on it, it will take you to a page with more information on that topic.

1. THE BEST TYPES OF IMMUNE CELLS TO TARGET ARE IN SURFACE-MOUNTED MUCOSAL LYMPH NODES CALLED “MALT PATCHES”

We believe the best way to administer vaccines is by directly applying topical mucosal vaccines (i.e., with the vaccine particles suspended in a nasal spray, or embedded in lozenges or lollipops, rather than injections) to a set of specialized lymph nodes that are fully exposed, and directly accessible, on the outer surfaces of mucous membranes. Those types of lymph nodes are called “MALT patches”, and they include the tonsils and adenoids, in humans and other large animals.

The immune cells in MALT patches offer two crucial advantages, over any other route we know of: (1) the particles in topical mucosal vaccines can contact those immune cells immediately, directly, and in large numbers, in ways that may lead to the fastest-acting vaccines ever created (which could be especially useful when an epidemic is gathering momentum); and, (2) if vaccine particles are pulled in via MALT patches, they can trigger and drive the formation of not just one, but two crucial types of antibodies. In addition to the Y-shaped internal (IgG) antibodies that injected vaccines can trigger (and which everyone has already heard about), if vaccines enter the body through a MALT patch, they can ALSO trigger the creation of an entirely different class of “secreted mucosal IgA antibody dimers”. Almost no one (other than physicians, and

immunologists) has ever heard about those types of secreted antibody dimers, but they have the potential to provide huge benefits that have not been available before now, especially against "upper respiratory tract" infections (such as COVID, influenza, pneumonia, etc.), and sexually-transmitted diseases (such as herpes, AIDS, hepatitis, gonorrhea, etc.) Secreted mucosal IgA antibody dimers are described in more detail **HERE**.

2. THE BEST WAY TO IDENTIFY POTENT "MALT-TARGETING TRANSPORT PEPTIDES" IS BY USING A "SCREENING TEST" ON A "PHAGE LIBRARY"

We believe the best way to identify peptide sequences which can be used as "MALT-targeting transport peptides" – which can potently trigger intake and processing – of vaccine particles having those transport sequences, on their outer surfaces – by immune cells in "MALT patches" (i.e., on the outer surfaces of surface-mounted lymph nodes – is by screening hundreds of millions of "candidate" or "contestant" phages, from a preparation called a "phage display library" (or simply a "phage library").

Phages (originally called bacteriophages) and phage libraries are described **HERE**. It took decades to develop good "phage display libraries," but now, anyone can buy one for less than $1000. The most widely-used versions use "filamentous" phages which are comparable to a flexible arm, with five long finger-like "tentacles" extending out from one end, which hunt for and grab hold of a bacterial cell, which a phage will try to infect, and hijack, to make more phages. All of the billions of different phage particles in a library are identical, EXCEPT FOR a randomly-generated sequence of 12 amino acids, which have been attached to the outer tips of all five of the long finger-like proteins, in a manner analogous to gluing rhinestones onto all five fingernails, on a hand . . . except for a crucial fact: a small number of truly valuable gems have been sprinkled in, among the billions of rhinestones.

"Screening tests" are a specialized category of tests, which scientists create and use, to try to identify those few phage particles that happen to be carrying "important and useful peptide sequences" (i.e., the valuable gems, hidden in huge piles of unhelpful rhinestones), among the billions of different phages in a phage library. A scientist who wants to find new peptide sequences which can perform "the XYZ trick" will try to think up some new way to use an affinity column, a batch of cells, some type of tissue culture, or a live animal (usually a fruit fly, mouse, or rat), to identify and somehow isolate (and then analyze) those few phages which happen to be carrying foreign peptide inserts that can perform the type of interaction the scientist is looking for. More information on screening tests is available **HERE**.

As the science progresses (with AlphaFold and AI being two major components), scientists can (and will) use computer models to try to predict which peptide sequences are likely to work well at various tasks. However, one of the hurdles that computer

models cannot deal with adequately is the question of whether the best-performing peptides, in some computer model, are likely to bind to or react with non-targeted proteins and/or cell types, either before they accomplish the desired task, or in ways that create unwanted side effects. Therefore, it can be more effective (and enlightening) to simply give millions of phages a fair chance to compete against each other, to see which ones will do best, in actually performing a desired task. So, that is how "screening tests" are designed and run.

And, pitting millions of "candidate/contestant" phages against each other, in a fair contest to see which ones actually work best, is even better, in this setting, since the goal is to identify phages which can trigger and drive – all the way to completion – not just one or two specific cell responses, but an entire sequence of 5 different steps, which must be performed by two very different types of immune cells, as described in the next section. No computer model can do something like that, as well (or as reliably) as simply giving the phages a chance to show what they can do.

3. THE SCREENING TEST WE CREATED CAN IDENTIFY PEPTIDE SEQUENCES THAT WILL DRIVE AN ENTIRE SERIES OF FIVE RESPONSES, BY TWO DIFFERENT TYPES OF IMMUNE CELLS, ALL THE WAY TO TRANSFORMING AN "IMMATURE" DENDRITIC CELL INTO A "MOBILE ANTIGEN-PRESENTING CELL". THAT IS A PERFECT PLATEAU TO AIM FOR, AND REACH, IN A SCREENING TEST.

To understand the statement above, readers need to know that surface-exposed "MALT patch" lymph nodes contain two crucial types of immune cells, which "internal" lymph nodes do not have. The "sampling" cells on the outer surfaces of MALT patches are called "M cells" (from "membrane" or "microvilli"). If their surface receptors detect what appears to be a "pathogen pattern" on a particle which contacts them, they will grab that potential/apparent/likely pathogen, and pull it in, inside a membrane bubble called a "phagosome". However, rather than processing that phagosome, an M cell will actively hustle and push it through the cell (that process is called "trans-cytosis"), and press it against the "basal" membrane on the underside of the cell. When those two membranes merge, that merger will eject the particle out of the cell, in naked/exposed form again, into a "docking site" that holds a dendritic cell.

Dendritic cells are the "genius-caliber" cells which control how an immune system will respond to "non-self" particles. They are too complex for a summary in this first page of this website, so they are described in more detail **HERE**. The main point that needs to be recognized, to understand the header above, is that when a dendritic cell – waiting, in the docking site of an M cell, for a particle to be delivered to it by that M cell – receives such a particle, ***it must make a yes-or-no, all-or-nothing "commitment" to one of two mutually-exclusive options:***

OPTION 1: if a particle appears to be a pathogen that is both dangerous and important, the dendritic cell will initiate and trigger an antibody-forming response, which will require that cell to undergo a major change, and then leave the docking site, to go off in search of the B and T cells which can perform the next steps in that response;

– or –

OPTION 2: if a particle appears to be common, run-of-the-mill, and not really dangerous, the dendritic cell will pull it in, digest it, and release its "building block" molecules, while staying in the docking site, to await the next particle delivery.

Therefore, the goal of the screening test which we have developed – which will involve 10 to 20 million phage particles, "infused" (using droplets from a micro-pipette, rather than needles) into the nostrils of each mouse or rat used in the tests – is to identify those few phages which happen to be carrying foreign inserts which appear to be so dangerous, and so important, that they will potently and rapidly trigger, and then drive, all the way to completion, every step in a series of five different cellular responses. The first three steps must be performed by M cells; as summarized above, they require: (i) intake; then, (ii) "trans-cytosis"; and then, (iii) ejection into a docking site, by an M cell. The final two steps require: (iv) analysis, by a dendritic cell; and, (v) an irreversible, irrevocable commitment, by that M cell, to transform itself in a way that will launch an antibody-forming response.

In other words, the "winning" phages in the screening test we have developed will be those phages will happen to be carrying foreign peptide sequences that we have nicknamed, "***HYPER***-pathogen peptides". Those pathogen-signaling peptides must make any phages – or, any vaccine particles – carrying those signaling peptides, appear to be so infective, and so dangerous, that they will be able to trigger and drive – within only about 90 minutes – M cells to pull them in, hustle them through, and hand them off, directly to dendritic cells, and then – still within the 90 minute limit – they must also provoke "immature" dendritic cells to fully commit to analyzing them carefully, and to then commit, irrevocably, to the type of transformation (aka maturation or activation) that will launch an antibody-forming process.

Because that is exactly what – in an ideal world, with ideal vaccines – vaccine particles should be designed to do, and should be able to do.

We also believe that the transformation of an "immature dendritic cell" into a "mobile antigen-presenting cell" is the perfect target, step, and plateau to aim for, in our screening test. When that transformation occurs, everything changes. It is entirely reasonable to state that . . . when an "immature" dendritic cell, commits to transforming into an antigen-presenting cell, well . . . ***THAT*** *is the moment when an antibody-forming response begins, within an animal's immune system*.

Therefore, if each vaccine particle is carrying only a small and limited number of "MALT-targeting transport peptides" (such as somewhere from about 10 to about 30 copies per particle, prominently displayed on the outer surfaces of each vaccine particle), while carrying ***multiple hundreds of copies*** of an "***antigen***" sequence (derived from a surface protein on the type of disease-causing microbe which that vaccine is designed to protect against), then a very large majority of antibodies that will be formed, will bind to the antigen sequence, rather than the transport sequence. And, that means that *any antibodies that are created, in response to the **ANTIGEN** sequence on the **VACCINES** . . .* will *ALSO be able to bind directly to the pathogenic microbe itself* (since it will have the same "antigen" sequences, on its surfaces), if that pathogen ever tries to invade and infect a vaccine-inoculated animal . . . or human).

4. THE BEST WAY TO IDENTIFY "IMMATURE" DENDRITIC CELLS THAT HAVE TRANSFORMED – INTO "MOBILE ANTIGEN-PRESENTING CELLS" – USES A CRUCIAL "TRANSLOCATION" WHICH MOVES CCR7 RECEPTORS FROM INSIDE THE CELLS, TO THE OUTER SURFACES OF THOSE CELLS

To understand the behavior of dendritic cells, one must understand the crucial role of a very unusual protein, called the CCR7 protein. One of the things that makes it so unusual is that it has *two cysteine residues, directly next to each other* (which led to the "CC" portion of the name). Cysteine residues have a highly reactive "side group" (called a sulfhydryl group, -S-H) which can react with a second sulfhydryl group, on a different cysteine residue, to form a strong and durable bond, called a disulfide bond. Those bonds – usually between two different cysteine residues that are located well apart from each other – play crucial roles in creating and then maintaining the three-dimensional shapes (also called conformations) of proteins. The shapes of proteins are crucial to their ability to perform their roles; therefore, cysteine residues (and the disulfide bonds) they form, are crucial, in protein shapes, structures, and interactions.

When an "immature" dendritic cell is first formed, multiple copies of the CCR7 protein are hidden inside the cell, where they cannot be contacted by any molecules outside the cell. That allows that cell to remain in a docking site beneath an M cell for as long as it takes, until it detects that some particle which has been delivered to it – by the M cell which owns and controls that docking site – is important enough to merit an antibody-forming response.

And, when that happens, that dendritic cell will "translocate" its CCR7 proteins from inside the cell, to the outer surfaces of the cell.

And, when that happens, those CCR7 proteins become "surface receptors", which can be contacted, and activated, by a chemo-attractant signaling molecule called CCL19 (which also has two cysteine residues, directly next to each other).

An "activated" (aka "transformed" or "maturing") dendritic cell will always travel in the direction of the largest number of signals it is getting, from CCL19 signaling molecules which are contacting and triggering the CCR7 proteins, which are distributed around the entire outer surface of the cell. That mechanism enables "activated" dendritic cells to travel toward, and eventually find and enter, "germinal centers" inside lymph nodes. T cells located in those germinal centers slowly and constantly release CCL19 molecules; and, since they are the source of that chemo-attractant, the highest concentrations of those signaling molecules will eventually lead "activated" dendritic cells to a source of the chemo-attractant, in a process called "climbing the gradient".

That completes an overview of the main facts and factors that have guided our work. A summary of the screening test we created – which uses those factors – is provided on the next page.

IF YOU WANT TO GET IN TOUCH WITH US . . .

If you want to contact us, click on the red heading directly above, and write a short message in the box on the page that will open, to let us know who you are, what you want us to know, and how we can get in touch with you.

The two PDF buttons below will enable anyone to download, at no charge: (i) a complete copy of this website, in pdf format; and, (ii) the entire Background section, and list of cited references, from one of several pending (but not-yet-published) patent applications that describe and claim MALT-targeting vaccines, and the methods used to create them.

This button will allow anyone to download a complete copy of this website, in pdf form.

This button will allow anyone to download the entire Background section, and list of references, from a not-yet-published patent application which describes and claims MALT-targeting vaccines.

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THE SCREENING TEST WE CREATED USED CCL19 AS A CHEMO-ATTRACTANT, TO ISOLATE DENDRITIC CELLS WHICH HAD ALREADY MOVED THEIR CCR7 RECEPTORS TO THEIR OUTER SURFACES.

When the facts and factors described on the previous page are explained in a logical step-by-step manner, focusing on each step that will lead to the desired result,

while excluding anything that might distract from a challenging pathway, that pathway might seem "obvious", as that term is used in patent laws around the world.

However, the startup company which owns this website – and, the patent rights to this invention – will state without apology that these insights did not simply "arrive". They could not be assembled, logically, until we figured out which facts were truly important, and then, how we could assemble them into a logical, step-by-step system while also eliminating other factors that would prevent or entangle what we were trying to do. We spent literally years, patiently and persistently trying other approaches, which didn't work, before we finally noticed several things that were well off to the side of the pathway we originally tried to follow. And, ***that*** was when we became ready, and able, to combine multiple different insights, components, and relationships, into a cohesive system that can actually work.

And so . . . we figured out how to use the CCL19 chemo-attractant as a motivating factor (or bait, lure, incentive, or however you might wish to phrase it), within a custom-designed, custom-assembled device which created a "challenge" which could be met and overcome, only by dendritic cells which had already moved their CCR7 receptors from inside the cell, to the outer surfaces of the cell.

We offer that much info as a bit of a game-playing exercise, to invite any reader to pass on and pose that challenge to any experts they know, who deal with ways for separating biological things. We invite and encourage any experts to spend a few moments, trying to figure out how THEY would isolate just those dendritic cells that have become activated/transformed, from a mixed batch of any surface and near-surface mucosal cells that could be extracted from a nasal airway in a mouse or rat. And, we challenge anyone to figure out, not just a "theoretically possible" way to do that, but the simplest, most direct, and most straightforward (and, therefore, probably the most reliable and consistent) way to do it.

Regardless of whether anyone tries to figure out how *THEY* would do it, the method *WE* settled upon is described **HERE**, as a step-by-step narrative summary. And, on that same web page, we offer to send the exact detailed recipes, for each and all of the steps, to anyone who is interested in, and capable of, repeating that type of screening test.

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ADVANCES AND BREAKTHROUGHS THAT ARE LIKELY TO RESULT, IF "MALT-TARGETING PEPTIDES" CAN CREATE THE WORLD'S FIRST "PRECISION-GUIDED VACCINES"

AND, ANALOGIES WE USE, TO HELP EXPLAIN WHAT WE ARE DOING.

We use two analogies, to help people develop a quicker and better mental grasp of what we're doing, and why.

The first analogy is this: it usually takes **only a few locomotive engines** (such as, about 5), to pull a long freight train, with up to about 200 freight cars, fully loaded with freight (at least, across normal terrain).

In similar ways, it will take only a small number of "targeted transport peptides" to make mucosal vaccine particles appear to be dangerous and important pathogens, which need to be pulled in and processed, by immune cells which can do exactly that, as quickly as possible. So, this approach can create a "transport platform, or system" which can be used to deliver ***ANY*** selected antigen/epitope sequence, from ***ANY*** pathogen that any vaccine company wants to study, in ***ANY*** type of animal. And, mucosal vaccine particles can be created which can carry, for example, only about 15 to 30 "targeted transport peptides", while carrying ***hundreds*** of copies of ***any*** selected antigen sequence.

To continue the train analogy, any company that wants to ship any type of freight, via train, can choose and use ***any type of freight car that is well-suited for that type of freight***. Companies that want to ship freight by train can use flatbed cars, boxcars, tanker cars, coal cars, "hopper cars" (for grains), container cars (for trucking containers), or any other type of specialized freight car.

In similar ways, ***any*** vaccine company can select and use ***any*** type of "core particle" it wants to use, from among multiple types of candidate particles (including, for example, phage viruses, disarmed adeno- or other viruses, virus-like particles, killed bacterial cells, etc.). And, any vaccine company can select and use any of numerous chemical, enzymatic, Spy-Tag/Catcher, or other attachment methods, to attach controllable numbers of "targeted transport peptides" to the surfaces of its vaccine particles. *Options for core particles, and for attachment methods, are summarized and reviewed in the "Patent Background" file, which can be downloaded at no cost via the PDF button in the bottom right corner of the home page of this website.*

Another analogy we offer, to try to help people develop a better mental grasp of what we're doing (and why), is this: ***injecting a vaccine into a muscle is like dropping hundreds of "dumb bombs", out of airplanes flying six miles high, in the hope that SOME of those bombs will hit the actual target(s)***.

By the time the Vietnam War ended, America's military and political leaders realized that no enemy country will ever be turned into an ally, by dropping more and more bombs on its people, and on the places, homes, fields, factories, and other things they need, to make a living, get food, and raise their children. So, experts in electronics, computers, physics, telecommunications, and other areas spent roughly thirty years, figuring out how to create and use "***precision-guided munitions***", which eventually led to laser-tracking and video-controlled rockets and then drones, which could hit a single targeted building, and then, a single moving vehicle, and now, a single targeted person.

And, as the war in Ukraine has proven, ***those advances have changed the very nature of modern warfare***. Why should, and why would, any country send young, trained, capable, and highly expensive and costly soldiers to be simply killed, by remote-controlled devices, when it can fight using devices, instead of troops? For anyone who has not been keeping up with how the war in Ukraine is being fought, two facts are offered, to help them better understand how "modern and future warfare" has been changed, by "precision-guided munitions". ***Fact 1:*** the average, typical, measurable life expectancy, of a Russian soldier who walks onto an active battleground or contested zone, in Ukraine, is now estimated to be ***about 30 seconds***. In other words, within about 30 seconds, any young soldier that Russia has paid dearly, to train, feed, equip, and prepare, will be killed – very, very quickly, if the Russian army is stupid enough to send him marching or running across some open field – by a drone (or swarm of drones) that Ukrainians have learned how to use, as true masters of that particular type of contest. ***Fact 2:*** as of mid-2026, multiple reports have stated that when US soldiers go up against Ukrainian soldiers, in simulated high-tech battlefield conditions . . . the Ukrainians win. Every time. It isn't even a fair contest. The Ukrainians have become so skilled, at using drones for fighting, that they are now the best in the world. And, every country in Europe knows it. They no longer ask US specialists to help train their troops; instead, they ask Ukrainian troops – who have actually figured out, and know, how to use "precision-guided munitions" – to train their troops, and show them how to get ready for any future invasions, or wars. As quoted by a high-level defense expert for one of the major European countries: "We don't think the Americans have anything they can teach us, that is worthwhile, any more. Not with ***these*** kinds of weapons."

FOUR POTENTIALLY HUGE ADVANCES AND ADVANTAGES, FROM "PRECISION-GUIDED VACCINES"

We have not just one but four powerful reasons – based solidly on science, and on what scientists know about how the immune cells that are involved do their work – for not just hoping, but anticipating and believing, that "precision-guided vaccines" will, within the next 10 years, disrupt, change, and modernize vaccine technology, vaccine usage, vaccine efficacy, and disease prevention, as profoundly as "precision-guided munitions" have disrupted and changed modern and future warfare.

Stated as predictions – which we fully anticipate will be used to measure, and tell the world about, whether we succeeded, or failed – we believe "MALT-targeting precision-guided vaccines" will, within the next 10 years, be able to accomplish each of four major objectives, which are listed below, in their likely order of importance.

As a crucial caveat, we ask any actual experts to NOT assess or comment on these predictions, based only on the capabilities of our startup company, alone. Instead, we ask them to evaluate whether we have made any mistakes or misinterpretations, about what M cells and "immature" dendritic cells (in MALT patches) can and will do, and how they are most likely to respond, if they are contacted – directly, and in fairly large numbers –

by mucosal vaccine particles that have "MALT-targeting peptides" (as described herein) attached to their surfaces. That is, after all, how science works. The "first person to notice and recognize something unusual" almost never gets it completely right, on the first try. Instead, because of how science works – when done properly – the most valuable service the "first person who gets there" can perform, is to figure out how to unlock a gate, and then call attention to the fact that a previously locked gate is now unlocked. It is the combined and cumulative efforts of those who then go and at least begin looking through that gate, to try to see what might be on the other side of it, that will determine whether something succeeds, or doesn't. There is a "Plans & Goals" button in the footer, at the bottom of each page in this website, and we ask anyone to read the page it leads to, before deciding how to evaluate, or respond to, any statement, anywhere in this website.

1. If "MALT-targeting" peptides can indeed help mucosal vaccines be pulled in and processed, in faster and more efficient ways, by both M cells and immature dendritic cells in MALT patches, then those types of vaccine particles probably will be able to trigger and drive the formation of, not just the Y-shaped internal IgG antibodies that can be triggered by injected vaccines, but also, ***SECRETED MUCOSAL IgA ANTIBODY DIMERS***. As described elsewhere, *THERE ARE MORE THAN TWICE AS MANY SECRETED IgA ANTIBODY DIMERS, IN JUST THE FEW POUNDS OF SALIVA, NASAL MUCUS, LUNG FLUIDS, AND DIGESTIVE JUICES, THAN ALL OF THE INTERNAL Y-SHAPED IgG ANTIBODIES IN THE ENTIRE REMAINING BULK AND WEIGHT OF AN ADULT HUMAN. THAT IS A TRULY POWERFUL INDICATOR OF HOW IMPORTANT THOSE SECRETED ANTIBODY DIMERS ARE*. For complex reasons, secreted mucosal antibody dimers can do more actual good than internal Y-shaped antibodies, at blocking the mucosal surface "beachheads" where most pathogens establish an initial infection, and begin reproducing, so that their progeny can begin moving and penetrating deeper into the body of a victim. However, until now, as described **HERE**, immunologists simply have not been able to find any consistent, reliable ways to create vaccines that will effectively trigger the formation of the types of secreted mucosal antibody dimers that can block the earliest stages of infections by mucosal pathogens.

2. They are likely to become the fastest-acting vaccines that have ever been created, for two reasons: (i) our tests to date show that phages with MALT-targeting peptides can cause ***"immature dendritic cells" to fully convert into "mobile antigen-presenting cells" within only 90 minutes after infusion of the phages, into the nostrils***, begins; and, (ii) when those newly converted dendritic cells leave the docking site behind an M cell, and begin searching for a germinal center inside a lymph node, ***they will already be inside a lymph node***. Now, why is "fastest" such a potentially important and valuable trait? Because, during a major epidemic (and even more, during a raging pandemic), or when such an event appears to be beginning to gather steam, faster vaccines are likely to be able to provide huge and crucial advantages, by minimizing the number of people who will become infected, and by minimizing the huge and horrible costs (including risks to caregivers) of caring for those who have become infected.

3. If “MALT-targeting precision-guided vaccines” can be made to work in the ways we believe they can, they will be able to completely eliminate any need for the types of noxious, irritating, inflammatory “adjuvant” additives that must be added to injected vaccines. As described elsewhere, adjuvants do their work by irritating the muscle cells, at the site of an injection, so severely, that those muscle cells will rapidly begin sending out distress signals, in the form of cytokine messenger molecules, which will recruit any nearby immune cells to hustle to the site of the injection, as quickly as possible, so that they can encounter and begin processing the vaccine particles before those vaccine particles are degraded, diffused, or taken in by the cells they contact. Under the current technology, that nasty and painful mechanism is necessary, to make injected vaccines more potent, more effective, and better able to protect larger numbers and higher percentages of the animals and humans that are inoculated by those vaccines.

That third major advantage merits an additional comment. In any other setting, if someone else could find some way to eliminate any need for the types of noxious and inflammatory adjuvants that must be added to injected vaccines, to make them more effective, that would be hailed by experts as a major, major advance, advantage, benefit, and blessing; and, such vaccines likely would be given a new category label, such as “Post-Adjuvant Vaccines”, to proclaim the marvelous and wonderful beginning of a new era, and a new generation, of vaccines.

Therefore, it says something important, about how we regard the even larger and even more important first two listed potential advantages of “Precision-Guided Vaccines.” In our frame of reference, we believe the possibility of eliminating irritating and inflammatory adjuvants, only rises to a level of getting rid of reasonably minor and tolerable levels of irritation. So, that advantage – which would have been a huge, massive, create-a-new-era accomplishment, for anyone else – ranks only third, in our assessment of the improvements and advances that we hope for, and anticipate, from our new types of vaccines.

4. And, finally, as the fourth major advantage, “precision-guided vaccines” will be able to completely eliminate needles, and nearly all other hazardous medical wastes that modern vaccines create. Instead of syringes, needles, and the other “detritus” that injected vaccines create, our vaccines can be embedded in a set of three or four lozenges, to be taken at least 6 hours apart (for a sustained-release dosage), with nothing but a small plastic wrapper, to hold the lozenges. And, they also can greatly reduce any need for refrigeration, or other special handling (which, among other advantages, will make them MUCH better suited for remote and/or tropical areas).

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LIST (WITH SUMMARIES) OF PAGES WITH

ADDITIONAL SCIENTIFIC INFORMATION

TO HELP EXPLAIN OUR APPROACH

This page contains a list, with brief overviews, of topics that are addressed in more detail on the pages that follow. **If you click on any red header, below, it will take you to a page with more info on that topic.**

1. BRIEF INTRODUCTION TO MUCOSAL MEMBRANES, AND MUCOSAL PATHOGENS

Mucous (or mucosal) membranes are very different from dry skin, aka "epidermis". Epidermal cells actually are empty pseudo-cells, created not by cell division, but by special precursor cells that expand rapidly, and then "pinch off" the expanded portion. That makes them ideal for absorbing and entrapping infective microbes, to prevent them from reproducing. By contrast, mucosal membranes are covered by complete and functional "epithelial" cells. As a result, they are major and constant targets and goals, for pathogenic microbes. "Mucosal pathogens" are – by far – the largest and most important class of pathogens; there are thousands of different types, compared to only a small number of "blood-borne" diseases transmitted by insect bites.

2. MALT PATCHES, AND HOW "M CELLS" SAMPLE AND PULL IN APPARENT PATHOGENS

MALT ("mucosal associated lymphoid tissue") patches are specialized lymph nodes, mounted on the outer exposed surfaces of mucous membranes. They are a crucial "first line of defense" against pathogens that try to infect mucous membrane cells.

M cells are "sampling cells" on the surfaces of MALT patches. If they detect a particle carrying a "pathogen pattern", they will grab it and pull it in, via a process called either "endocytosis" (a broader term) or "phagocytosis" (limited to particles, and excluding droplets); and, to protect the cell, the particle will be enclosed in a small membrane bubble, called an "endosome" or "phagosome". Rather than processing it, an M cell will push that type of phagosome through the cell as rapidly as possible, and press it against the "basal" membrane of the M cell. When those two membranes merge, it will eject the particle (in naked/exposed form) into a "docking site", which is a cup-shaped structure on the bottom of the M cell. A type of immune cell called an "immature" or "pre-committed" dendritic cell – will be waiting, in that docking site, for that type of "pathogen delivery" by the M cell.

Therefore, “MALT-targeting” peptides are “pathogen pattern” peptides that can be attached to the surfaces of vaccine particles, so that they will “trick” the M cells into pulling them in, and passing them on to dendritic cells that are waiting for pathogen deliveries.

3. DENDRITIC CELLS ARE THE “GENIUS” CELLS WHICH CONTROL ANTIBODY-FORMING RESPONSES. THEREFORE, THEY ARE THE PERFECT TARGETS FOR “TARGETED TRANSPORT” VACCINES CARRYING PATHOGEN SIGNALS WHICH MAKE THOSE VACCINE PARTICLES LOOK LIKE DANGEROUS PATHOGENS.

Dendritic cells play the crucial role in determining: (i) which foreign particles are NOT really important and dangerous, and should be gobbled up and digested on the spot, without further ado; versus (ii) which foreign particles appear to be dangerous and important pathogens, which need to be taken to a lymph node (while being broken apart and semi-digested along the way), so that T and B cells in a lymph node can make antibodies that will bind to those alien/invading particles.

With the help of “chemo-attractant” signals, newly-formed dendritic cells find and settle into the “docking sites” on the undersides of M cells, to await a pathogen delivery that will cause them to transform from an “immature” dendritic cell, into an “antigen-presenting” cell. Therefore, “MALT-targeting peptides” - attached to the surfaces of mucosal vaccine particles - offer an ideal way to get those vaccine particles rapidly delivered to dendritic cells, and to get dendritic cells which receive those vaccine particles to do exactly what is needed, to launch an antibody-forming response to any antigens which are present (in large copy numbers) on the surfaces of those vaccine particles.

4. WHEN AN “IMMATURE” DENDRITIC CELL ENCOUNTERS A PATHOGEN THAT MERITS AN ANTIBODY-FORMING RESPONSE, IT MOVES MULTIPLE CCR7 RECEPTOR PROTEINS FROM INSIDE THE CELL, TO THE OUTER SURFACE. THE CCR7 RECEPTORS CAN THEN BE CONTACTED BY A CHEMO-ATTRACTANT CALLED CCL19, WHICH GUIDES ACTIVATED DENDRITIC CELL TO “GERMINAL CENTERS” INSIDE LYMPH NODES.

When dendritic cells are first formed, they are actively recruited, by a chemo-attractant cytokine released by M cells, to travel to and settle into “docking sites” on the “basal” sides of the M cells. Large numbers of dendritic cells go to those docking sites, to wait for “pathogen deliveries” by and from those M cells. They can remain in those docking sites for as long as necessary – i.e., until something “activates” them – because their CCR7 receptor proteins remain inside those “immature” cells, and cannot be contacted by any signaling molecules.

That changes, dramatically, when an immature dendritic cell receives and analyzes a particle, and determines that it appears to be sufficiently dangerous and important to merit an antibody-forming response.

When that happens, the cell will "translocate" its multiple CCR7 receptor proteins from inside the cell, to locations distributed around the outer surface of the cell. After they reach the surface, those CCR7 receptors will be triggered by a chemo-attractant molecule called CCL19.

CCL19 is constantly being secreted and released by T cells inside the germinal centers of lymph nodes, and it provides the signals that enable activated dendritic cells to travel toward a lymph node. An activated dendritic cell will always travel in the direction of the highest concentration of CCL19 (that process is often called "climbing the gradient").

When it finally reaches a "germinal center" inside a lymph node, a dendritic cell will present semi-digested "chunks" of protein (from the surfaces of the foreign particle) to T and B cells. The T and B cells will then begin working together, to create antibodies that will bind to those foreign protein sequences. The dendritic cell will leave the lymph node, once its task is finished, and in some cases it might convert back into "immature" status again.

5. THE "TRANSLOCATION" OF CCR7 RECEPTORS FROM INSIDE AN IMMATURE DENDRITIC CELL, TO THE OUTSIDE OF THAT CELL (WHEN IT MATURES/ACTIVATES/TRANSFORMS INTO AN "ANTIGEN-PRESENTING CELL") OFFERS A DIRECT WAY TO IDENTIFY "MALT-TARGETING" PEPTIDE SEQUENCES (aka *HYPER*-PATHOGEN PEPTIDES), BY USING A NEW "SCREENING TEST" ON CANDIDATES FROM A "PHAGE DISPLAY LIBRARY".

After the physiologist employed by Precision-Guided Vaccines LLC learned about (and recognized the importance of) how CCR7 receptors are "translocated" when a dendritic cell becomes activated, he figured out how to create and use a new type of "screening test", on candidate particles from a "phage display library" (as summarized in the next topic, directly below). That new type of screening test uses the CCL19 chemo-attractant to isolate only those dendritic cells that had become "activated", by contact with phage particles which happened to be carrying foreign peptide sequences which made those "winning" phage particles appear to be infective, and dangerous.

The steps and the reagents that were used, in that new type of screening test, are described **HERE**. As a super-condensed summary, mixtures of phage-exposed mucosal cells, from mice, were loaded into the top chambers of vertical tubes, sitting in wells that contained the CCL19 chemo-attractant. That created a dual-chamber separating device, with a filter having 5-micron pores separating the mucosal cells (in the top chamber)

from the CCL19 chemo-attractant (in the bottom chamber). The liquid level in the wells was high enough to enable the CCL19 to begin diffusing upward, through the filter, and begin contacting the mucosal cells, as soon as the tube-with-filter device (with phage-exposed mucosal cells, sitting on top of the filter) was lowered into the well.

The ONLY cells that were both ***MOTIVATED . . . and ABLE*** . . . to squeeze through those 5-micron pores, to get to the bottom chamber (i.e., to reach the higher concentration of CCL19 below that filter), were dendritic cells ***which had become activated, and which had moved their CCR7 receptors to their outer surfaces***.

After 2 hours, cells that had reached the bottom chamber were collected, and then broken apart by a detergent that breaks up cell membranes, but does not affect the proteins that cover the phages. Whatever the cells released, when broken apart, was "plated" at low density, across agar plates with fresh host bacteria. Within 2 days, a small number of clonal phage colonies began to appear on the plates. Those clonal isolates were extracted, replicated in new host bacteria, and analyzed, to find out what amino acid sequences they were carrying in their foreign inserts. Those amino acid sequences were identified as "*HYPER*-pathogen peptides" that were able to trigger, and then drive, all the way to completion, not just one, but an entire sequence of responses, by not just one but two different types of immune cells, which work together and cooperate beautifully, in the surface-mounted lymph nodes called MALT patches.

6. PHAGES, "PHAGE LIBRARIES", AND "SCREENING TESTS" THAT CAN BE USED TO ISOLATE THOSE FEW PHAGES, FROM AMONG MILLIONS OF CANDIDATES, WHICH CAN TRIGGER SPECIAL TYPES OF REACTIONS.

A summary page which introduces phages, phage libraries, and screening tests, is provided **HERE**. As a very brief intro:

"Phages" (originally called "bacteriophages") are the smallest viruses ever discovered. Each type can infect only a small set of bacteria, and none can infect plants or animals, so they are treated as harmless and non-pathogenic.

Phage "libraries" (aka phage *display* libraries) contain billions of different phage particles. In the most widely-used type of library, each particle carries a single gene which has been engineered to carry a completely randomized (via chemical synthesis) sequence of 36 bases (12 codons, with 3 bases in each codon), which will encode a corresponding random 12-amino-acid peptide sequence. That "foreign insert" peptide sequence will be attached to the outer tips of all five copies of a long tentacle-like protein that the phages use to hunt for, and grab hold of, new bacterial cells which they can infect (this can be compared to gluing cheap rhinestones onto all five fingernails, on a hand, with a few valuable gems hidden among the billions of rhinestones). Good phage libraries took decades to develop, but now, a top-quality library with literally a *trillion* different

"candidate" particles (all in a single tube; they are *THAT* small) can be purchased for less than $1000.

"Screening tests" are clever ways, thought up by scientists, to subject several million phage particles (in each small batch that is tested in a specific "run") to a fair competition, usually involving something like, "Uptake and processing, by a specific and unusual type of cell". A well-designed screening test can enable scientists to isolate and then analyze those few phages which happen to be carrying an inserted/foreign peptide sequence which causes those cells to perform that activity (i.e., a screening test is designed to identify, and isolate, the rare valuable gems that are scattered among millions and millions of useless rhinestones). Rather than trying to predict, design, or control which protein sequences will be able to perform "the XYZ trick", it is often easier to design a way to let millions of phages give it a try, and compete against each other, and figure out some way to isolate those phages which were able to do that particular trick. Later, after number of "first round winners" have been identified, a way to perform a "second round competition" can be thought up, to figure out which ones, among the "first round winners", can perform the desired trick most potently, effectively, rapidly, or whatever. And, after a "winner" has been identified, various ways can be used to create and test controlled and/or random mutants having 1 or 2 altered amino acids, to see if any of those might be even more potent and effective than a "starting point" (or "referent") winner, at performing the desired task.

That completes a summary/overview of various facts and factors that had to be recognized and assembled, to create a way to identify "MALT-targeting" peptide sequences (also called "***HYPER***-pathogen peptides") which can be attached to the surfaces of mucosal vaccine particles, to cause those vaccine particles to: (i) be taken in, transported, and ejected into a docking site, rapidly, by M cells on the surfaces of MALT patch lymph nodes; and, (ii) be able to trigger the maturation (aka activation, or transformation) of "immature" dendritic cells, into "mobile antigen-presenting cells". The next pages contain more information on each of the topics listed above.

[NEXT PAGE]

TOPIC 1. BRIEF INTRODUCTION TO MUCOSAL MEMBRANES, AND MUCOSAL PATHOGENS

With only a few exceptions (mainly for "blood-borne diseases", such as malaria and Lyme disease, which are spread by insect bites), almost every disease-causing microbe on this planet evolved in ways that caused them to become "mucosal pathogens", which infect animals by penetrating into cells on mucosal membranes. Even if their main damage occurs in other types of tissues, they must establish an initial

infection, to establish a “foothold” (or beachhead, or similar terms) where they can begin reproducing, so that their progeny can then try to spread into other parts of the body.

Two major aspects of animal anatomy and physiology drove pathogens to mutate and evolve in that direction:

1. “Dry skin” is covered by “epidermal” cells, and those are not really “cells” at all; instead, they are empty-bag “pseudo-cells” which are dead from the moment they are created. Instead of being formed by cell division, they are formed by a “budding” process, in which precursor cells (located about 6-8 layers deep, in most areas of dry skin) rapidly enlarge to nearly twice their normal size, and then “pinch off” something which is basically an empty bag – with a normal outer membrane, having surface proteins which microbes can latch on to, but with almost nothing but slightly salty water inside that membrane. That makes epidermal cells ideal as “decoys” or “bait” for pathogens, which use their tricks and tools to break into those cells, only to discover that they have broken into an empty shell of a building, with none of the things they need, to reproduce, and none of the things they need, to escape.

2. By contrast, mucous membranes are covered by an entirely different class of cells, called “epithelial” cells. Those are full and complete cells, with all of the biochemical machinery and supplies that pathogens need, to reproduce. And unlike cuts, nicks, or wounds, which disappear fairly rapidly as they heal, mucous membranes are always available, and accessible, at all times, in any animal. Therefore, they are very tempting targets, for any type of pathogen which has evolved with some type of mechanism for grabbing hold of one or more types of epithelial cells, and then invading those cells (and, different types of microbes use a wide variety of such mechanisms).

Although most people are startled when they hear this number, the total area of the mucous membranes, in an adult human, is estimated to be about 200 times larger than the total area of dry skin, which covers the body. While that ratio might seem exaggerated or even preposterous, two factors help explain it:

(i) it includes all of the microscopically small sacs inside both lungs, when fully inflated to bursting pressure. That surface area, by itself, is (and must be) quite large, to provide enough gas transfer, across those membranes, to supply all of the muscles, organs, brain, and other tissues of the body with enough oxygen to keep them fully functioning, even under periods of strenuous exertion; and,

(ii) most mucosal surfaces have very large numbers of folds, ripples, invaginations, and other irregularities. Some are visible, but many more are microscopic in size. Those folds, ripples, etc., provide mucous membranes with numerous advantages, including remarkable flexibility and stretchability, as well as greatly expanded surface areas, which allow very large numbers of surface-mounted cells (and even specific types of cell surfaces) to perform specialized functions.

In addition, another huge advantage helped promote and enlarge the class of mucosal pathogens. If a pathogen can infect a surface mucosal cell and begin reproducing

in that cell, it almost certainly will be able to begin forcing that host cell to either: (i) die and split open, thereby releasing dozens, hundreds, and in some cases thousands of new copies of that pathogen; or, (ii) become "leaky", and begin secreting pathogens, in ways that keep the host cell alive, so that it will keep making even more copies of that pathogen. Since nearly all types of viruses and bacteria can reproduce very rapidly after they "set up shop" inside a host cell, the pathogens will be able to reproduce, and release multiple copies of themselves, long before all of the necessary steps can be completed to: (i) enable the infected cell to begin creating and moving distress-signaling cytokine molecules to its basal surface; (ii) enable a "killer T cell" to find that infected cell; and, (iii) wait for the killer T cell to engulf and destroy the infected cell. By the time all those steps can be completed, the infected cell is likely to be already dead, or actively spewing out copies of that pathogen. This is a major part of the reason why, even if someone has been vaccinated against COVID viruses, and has even been previously infected by COVID, if that person gets COVID again, s/he is likely to have very high numbers of active and infective COVID viruses, in his/her saliva.

With those and other factors actively encouraging the development of mucosal pathogens, animal immune systems had to develop a "first line of defense" against mucosal pathogens; and, "MALT patches", and a special type of secreted antibodies – with a completely different structure and function than classic Y-shaped internal antibodies – became two of the main components of that "first line of defense" against mucosal pathogens. Those topics are described on the next two pages.

[NEXT PAGE]

TOPIC 2. MALT PATCHES, AND HOW "M CELLS" SAMPLE AND PULL IN APPARENT PATHOGENS

The phrase "lymph node" refers to specialized tissue sites where T and B cells work cooperatively with each other, to create antibodies that will bind to chunks of proteins that are brought into the lymph nodes, by mobile "antigen-presenting cells." For historical reasons (described in the downloadable Background section of a patent application which can be found **HERE**), any cells which can create antibodies are called "B cells." T cells (which were given that name because they must pass through the thymus, which is inside the chest, and which is at a halfway point between an organ, and a gland) are the cells which manage, supervise, and control B cells which are trying to create the best possible antibodies. Among other roles, T cells give essential stimulatory molecules to B cells which are creating promising antibody candidates; and, they refuse to give those vital signaling molecules to B cells which are not making promising antibodies, so that the non-promising B cells will die off, and simplify the competition.

With that as the definition of "lymph node", the specialized immune system tissue patches that are exposed and accessible, on the surfaces of mucosal membranes (called

MALT patches, for “mucosal associated lymphoid tissues”) fully qualify as “lymph nodes”, since they do indeed contain B and T cells which work together, to create antibodies that will bind to alien/invading/non-self peptides that are presented to them by mobile “antigen-presenting cells”.

However, MALT patches usually are not called “lymph nodes”. Instead, they belong in a special category, which deserves its own special name, because they have additional roles, capabilities, and functions that internal lymph nodes cannot match.

And, as brief asides:

(i) MALT patches that occur in the nasal cavity or mouth are also called NALT patches, where the N refers to “naso-pharyngeal”, to include not just the nasal cavity, but also the pharynx (i.e., the place where the nasal cavity, mouth, and throat all come together and intersect); and,

(ii) MALT patches in the intestines are sometimes called GALT patches (where G stands for “gut”), but they are more commonly called Peyer’s patches.

The crucial difference between surface-exposed MALT patches, versus “internal” lymph nodes, arises from the presence and activities of highly specialized cells, called “M cells” (from either “membrane” or “microvilli”, depending on what sources you read).

The “lumenal” (also spelled luminal) surface of an M cell (i.e., the surface which is exposed to food and/or air, in the mouth, nasal cavity, and lungs, and to food which is being digested, in the intestines) will have surface-mounted receptor proteins that are constantly looking for “pathogen patterns”, on particles which contact those receptors; and, when one of those cell receptors recognizes a “pathogen pattern”, on a particle which has contacted the cell, the cell will pull that particle inside the cell, for processing.

Summarized briefly, “pathogen patterns” (they are a sub-category of a larger class of signaling molecules called “pathogen-associated molecular patterns”, or PAMPs) are protein sequences (i.e., specific sequences of the 20 “primary amino acids” which are strung together to make all proteins, in all forms of life on this planet) which appear on numerous different types of microbes. Those “pathogen pattern” sequences became “highly conserved”, and appear on numerous different types of microbes, because they mutated and evolved to a point where they reached a “sweet spot” of truly optimal functionality and efficiency, to a point where any other microbes, carrying different mutated versions of those “highly conserved regions”, will not be able to function as well, and will not be able to compete effectively against microbes having the optimal, highly-conserved sequences.

Accordingly, if an M cell, on the surface of a MALT patch, detects that a particle – which has been inhaled or swallowed – has one or more “pathogen patterns” on its surface, the M cell will pull that particle into the cell, using a process called “endocytosis”, or “phagocytosis.” As a brief aside, endocytosis is a broader term, because it also includes a second process called “pinocytosis”, which involves taking in tiny droplets of liquid. If *particles* are being pulled in by a cell, the term “phagocytosis” is more precise, and is preferred.

When “phagocytosis” occurs, the cell encloses an incoming particle inside a bubble

of membrane material, called a "phagosome", partly to isolate the cell against the risk of being attacked by the particle, and in many cases, to begin the process of digesting and breaking apart that particle. In nearly all cases involving cells other than M cells, intake of a particle, inside a phagosome, leads to digestion of the particle, by a two-step process: (i) special enzymes will begin pumping acid into the phagosome, to begin softening, prying apart, and loosening up whatever is in the particle, in a manner comparable to way stomach acidity gets chewed food more ready to be digested; then, (ii) a "lysosome" will merge with the phagosome, and that merger will add more acidity, and aggressive digestive enzymes, to the mixture, so that the particle can effectively be "cooked and dissolved" inside a bubble which protects the rest of the cell components from those very harsh conditions.

However, if phagocytosis ***by an M cell*** was triggered by a "pathogen pattern" on a particle which was pulled inside the cell, the M cell will shift into a very different mode, which is believed to be unique to M cells, and only M cells. Using a combination of microtubules and energy-donating enzymes, an M cell with a phagosome containing an apparently dangerous pathogen will actively push, pull, and hustle that phagosome, as rapidly as possible, toward the bottom surface (the "basal membrane") of the M cell. And, when the moving bubble of membrane material (which encloses the phagosome) gets pressed against the basal membrane of the cell, those two membranes will merge together with each other, since they are made of exactly the same types of molecules. When that happens, the "apparently dangerous particle" will be ejected out of the M cell, in "naked form" again, with no membrane surrounding it. That unique M cell process is called "trans-cytosis", which translates into "through the cell", or "across the cell".

And, that process will eject the particle directly into a special and unusual type of open and roughly U-shaped cavity, on the "underside" (or "basal" side) of the M cell.

Those cavities are called "docking sites", because they are functionally similar to the "docking sites" that big trucks will back up into, on the back sides of retail stores, to both: (i) deliver new products to those stores; and, (ii) carry away, for delivery, anything which is too large or heavy for customers in that store to carry away on their own.

And, those docking sites are extra-special, because that is exactly where large numbers of immature dendritic cells go to, in order to wait for a "pathogen delivery" by an M cell. They do that, because there is a specific "chemo-attractant" cytokine molecule which is slowly and constantly released, by M cells, into the docking sites on their basal surfaces. That chemo-attractant actively attracts *immature* dendritic cells, to those docking sites.

And, that leads into a discussion of "dendritic cells", on the next page.

[NEXT PAGE]

TOPIC 3. DENDRITIC CELLS ARE THE "GENIUS" CELLS WHICH CONTROL ANTIBODY-FORMING RESPONSES, TO

PATHOGENS THAT ARE EITHER IMPORTANT, OR NOT. THEY ARE THE PERFECT TARGETS, FOR "TARGETED TRANSPORT" VACCINE PARTICLES HAVING "PATHOGEN PATTERNS" WHICH MAKE THOSE VACCINE PARTICLES LOOK EXTREMELY DANGEROUS.

As an opening statement, dendritic cells rank in the "genius" league, when it comes to individual cells. *THEY* are the immune cells which must figure out which invaders are important, and which are not; and, when *THEY* determine that some particular (and apparently foreign, invading, non-self) particle is important, *THEY* are the cells which begin traveling toward a lymph node, to deliver that package to the B and T cells in a lymph node. The B and T cells inside a lymph node stay put, and can only wait for a mobile immune cell to show up with a chunk of "foreign" protein on an MHC mounting plaque, and then respond to whatever the mobile immune cell brought to them. So, it is dendritic cells, rather than T cells or B cells, that govern and control what the immune system will do, and how it will respond to foreign particles. Indeed, dendritic cells even determine and control whether the protein chunks from a foreign particle, will be mounted on MHC-1 proteins (which will trigger the creation of "killer T cells" that can engulf and destroy any particles having those peptide sequences on their surfaces), or whether the chunks of foreign protein will be mounted on MHC-2 proteins (which will trigger the creation of antibodies that will bind to those proteins).

Therefore, it is ***dendritic cells***, rather than B cells or T cells, which perform the ***absolutely essential, crucial, central role in determining what an immune system will respond to, and what it will not respond to***.

Therefore, ***if some new type of vaccine can get vaccine particles delivered directly to dendritic cells*** – and, if it can somehow "persuade" those dendritic cells, rapidly and reliably, that *THESE* vaccine particles are dangerous, and important, and merit a fast-as-possible launch of an antibody-forming response – that would be a remarkable accomplishment, and something worth serious attention, and careful study.

And, that is exactly what MALT-targeting vaccines can accomplish.

Backing up a bit, dendritic cells deserve a more comprehensive description, to help people better understand what they do, and how they do it.

They do not have eyes, and they cannot see anything; and, they do not have noses, or "olfactory receptor neurons", so they cannot "smell" things, in the way that animals with noses can smell things. What they use – instead of sight or smell – to find (and then travel toward) whatever they are looking for, at any given moment, is a cellular process called "chemotaxis". That type of cellular travel uses multiple surface receptors which

will be triggered and activated by “chemo-attractant” signaling molecules; and, those surface receptors are positioned at numerous spaced-apart locations, around the entire outer surface of each dendritic cell.

“Chemotactic surface receptors” are specialized proteins which “straddle” a cell membrane, with one portion in an exposed outer location – where it can be contacted by “chemo-attractant” signaling molecules – while another portion is inside the cell, so it can send signals to the biochemical “machinery” inside the cell. In nearly all cases, a dendritic cell (or any other type of “mobile” immune cell) will move in the direction of the highest apparent concentration of “chemo-attractant” molecules, as indicated by signals the cell is getting from the chemotactic surface receptors on whichever side of the cell is getting the most signals, at any given moment.

So, large numbers of newly-created “immature” dendritic cells use chemotaxis to help them locate, and settle into, “docking sites” on the “basal” surfaces of M cells, in MALT patches.

Why do they do that?

Because that is exactly where “immature” dendritic cells need to be, in order to be available, equipped, and ready to “spring into action”, when an “apparently dangerous particle” suddenly pops out of the basal membrane of an M cell, enters that “docking site”, and directly encounters the “waiting arms” of an “immature” dendritic cell.

The word “immature”, when applied to dendritic cells, needs to be explained, lest anyone assume they are not yet full-grown, or mature enough, or strong enough for the tasks they must perform.

None of those things are true; instead, “immature” dendritic cells are full-sized, fully-grown, and fully strong enough to “pick up arms, and march into battle”. However, they have not yet encountered a pathogen particle which is strong enough, and important enough, to change and transform their lives, forever. As an analogy, they are not like immature children who haven't yet reached puberty; instead, they are comparable to young men, aged 20-25, who are living in their parents' basements and whiling away their hours watching TV, texting, surfing the net, and playing video games, because nothing has “grabbed them” in a way that is strong enough to get them to move out, and begin living a “real” life. Accordingly, rather than calling them “immature” – which suggests negative things, including a lack of size, strength, skill, or capability – they could more accurately be called “pre-transformed”, or “pre-committed.”

The reference to “waiting arms of a dendritic cell” also merits a brief digression, to explain it. Despite the absolutely crucial role they play in launching antibody-forming responses, and in being in charge of telling the B and T cells exactly what antigen sequences they must respond to, dendritic cells were not even discovered, or known to exist, until 1973, when a fellow named Ralph Steinman recognized that a specific cell type that no one had paid attention to, previously, was much more active, and important, than anyone had previously realized. He won a Nobel Prize for that discovery, but not

until almost 40 years later, in 2011, and he remains, to this day, the only person who has ever been awarded a Nobel Prize posthumously.

As the discoverer, Steinman was entitled to name them, and he chose the name "dendritic", from a Greek root that refers to tree branches, and other "branching"-type extensions that become smaller, as they get farther from their source, and which tend to extend outward, rather than having an appearance like a batch of stirred limp noodles.

However, "dendritic cells" turned out to be an unfortunate name, for several reasons. One problem was that other types of cells (especially neurons) also contain branch-like projections that are also called "dendrites"; and, that overlap and conflict apparently blocked or prevented the emergence of a single-word name (such as dendricytes, or dendrocytes). Accordingly, the term "dendritic cells" became and remains the standard term, and whenever a physician or researcher hears that phrase, they must do a quick but distracting mental check to ask, "Are we talking about neurons, or immune cells, at this moment in time, and in this context?"

In addition, subsequent research (after Steinman had already assigned that less-than-ideal name to them) revealed that their "dendrites" are not actually tubular, and do not resemble the branches of trees. Instead, they have substantial width and flatness, and are more similar in shape to petals on a flower (or leaves on a "succulent" plant), than to branches on a tree. The wider, flatter shape provides the projections with more surface area, which is needed for large numbers of surface receptors, and for surface-mediated activities that are carried out by the cells. However, it also is worth mentioning that any comparison to the shapes of petals on a flower, or leaves on a succulent plant, requires yet another qualification. Rather than being firm, engorged, and "reluctant to yield or bend", they can shrink and collapse, if and when a need arises, and any liquid inside those protrusions apparently can be retracted, into the main cell body, if a need arises; and, that is yet another important trait and capability of dendritic cells, because that capacity is a crucial part of how they travel, or "migrate", if and when a need arises. They are capable of using a type of motion called "pseudopod migration", which is used by amoebas (and by octopuses, if they are challenged to squeeze through a small hole or gap, to get to a fish or crab). That type of travel enables dendritic cells to squeeze through the lymph-filled gaps between neighboring cells, in soft tissues.

Returning to the main subject, large numbers of newly-created "pre-committed" dendritic cells are actively recruited (via chemo-attractant signaling molecules) to find, and settle into, docking sites on the basal surfaces of M cells in MALT patches. Those docking sites are the perfect locations for newly-formed dendritic cells to go to, so that they will be ready to respond, quickly and directly, when an M cell pulls in an apparently dangerous particle (i.e., having a "pathogen pattern" on its surface), and rapidly transports that particle (isolated inside a phagosomal bubble) through the cell. When the M cell ejects that particle into its docking site (in "naked" form again, after the phagosome holding the particle merges with the "basal" membrane of the M cell), that particle will be delivered directly to the surface of a dendritic cell, which has been

patiently waiting for exactly that type of "pathogen delivery," by the M cell which created (and which controls) that docking site.

When a dendritic cell receives such a particle, it will use a complex and sophisticated set of numerous surface receptors to analyze that particle, and the cell will then "commit" to either of two very different options:

OPTION 1: If the particle appears to be routine, and not really important, the dendritic cell can simply take it in, break it apart (i.e., digest it), and release its "biochemical building blocks," so that other cells can use those building blocks for their own nutrition, and that "not-yet-activated, still-immature" dendritic cell can simply wait, without further ado or commotion, in that same docking site, for the next particle that will be delivered to it by that M cell;

– OR –

OPTION 2: if the particle appears to be a dangerous and important pathogen which merits a full-scale "antibody forming" response . . . then . . . that dendritic cell will "commit" to an "activation/maturing/transforming" event, which will become a major "life-changing" event, for that "previously immature" dendritic cell.

Accordingly, when a dendritic cell finishes analyzing a particle which has been handed to it by an M cell, the dendritic cell must choose between the two options described above. There are no other, alternate, "partial" or "halfway" options available. A dendritic cell must commit, fully and completely, to either activating, maturing, and leaving that docking site; or, it must remain in place, without making that transition. By way of analogy, when a train leaves a station, a person is either on that train, or not on that train; there are no halfway or partial options available (at least, not for people who are still alive, with all their limbs still attached).

WHEN AN "IMMATURE" (OR "PRE-COMMITTED") DENDRITIC CELL DETECTS THAT A PARTICLE DELIVERED TO IT BY AN M CELL IS A DANGEROUS AND IMPORTANT PATHOGEN WHICH MERITS AN ANTIBODY-FORMING RESPONSE, IT WILL "TRANS-LOCATE" ITS CCR7 RECEPTORS FROM INSIDE THE CELL (WHERE THEY CANNOT BE CONTACTED BY ANY CHEMO-ATTRACTANTS), TO MULTIPLE LOCATIONS AROUND THE OUTER SURFACE OF THE CELL. THE TRANSFORMED (aka ACTIVATED, MATURING) DENDRITIC CELL WILL THEN BECOME A "MOBILE ANTIGEN-PRESENTING CELL" WHICH WILL LEAVE THE DOCKING SITE, AND BEGIN SEARCHING FOR THE SOURCE OF A CHEMO-ATTRACTANT CALLED CCL19. THE CELL WILL ALWAYS TRAVEL IN THE DIRECTION OF THE HIGHEST CONCENTRATION OF CCL19 WHICH IS BEING DETECTED, AT ANY GIVEN MOMENT, BY ITS CCR7 RECEPTORS.

Therefore, if vaccine particles can be made to ***APPEAR*** to be extremely pathogenic, dangerous, and important – by placing one or more peptide sequences on them which, in nature, are on the surfaces of the most dangerous and important types of pathogens that exist in nature – then those peptide sequences can trick and fool dendritic cells into "believing" that those vaccine particles are indeed extremely dangerous and important. And, if that can be accomplished, then dendritic cells which receive those types of vaccine particles, as "pathogen deliveries" coming from M cells in MALT-patches, will rapidly and irrevocably commit to activation, maturing, and leaving the docking site which belongs to that M cell, to go find the germinal center of a lymph node, using the process called "antigen presentation."

That is exactly what an effective "MALT-targeting" sequence (as described herein) can do. A good and potent MALT-targeting sequence can (and will) cause surface-exposed M cells, in MALT patches, to actively pull in those apparently dangerous and important particles, rapidly push them through the M cell, and eject the particle (in naked form again), directly into the M cell's docking site, which will hold an immature dendritic cell. Once that has been accomplished, those same MALT-targeting sequences can (and will) cause immature dendritic cells (which are waiting for pathogen deliveries, in those docking sites) to interpret those "pathogen pattern" danger signals in ways that will rapidly drive those dendritic cells into a full and irreversible commitment, to convert into an activated/maturing dendritic cell, which will leave that docking site, and go off in search of a "germinal center" in a lymph node (i.e., a place where T and B cells wait for "antigen-presenting cells" to bring them new challenges).

Those are exactly the types of responses, by exactly the right types of immune cells, that will trigger, launch, and drive the type of antibody-forming response that vaccines particles are designed and intended to create.

[NEXT PAGE]

TOPIC 4. ANIMALS USE "SECRETED MUCOSAL ANTIBODIES" TO HELP THEM FIGHT OFF MUCOSAL PATHOGENS. HOWEVER, MUCOSAL ANTIBODIES HAVE ENTIRELY DIFFERENT STRUCTURES AND FUNCTIONS THAN INTERNAL ANTIBODIES, AND THEY ARE NOT TRIGGERED AND CREATED IN RESPONSE TO INJECTED VACCINES.

Vertebrate animals have two entirely different types of antibodies, to help them fight off pathogens and diseases.

Actually, vertebrates have six distinct type of antibodies, but most of them are not important, in actually helping fight off pathogens. So-called "IgE" antibodies are

generally unwanted, and are more involved in allergic reactions, than in defending against diseases. In a classic goof-up, the "IgM" name applies to two very different types of antibodies: (i) an extra-large ring structure, formed by coupling together 5 Y-shaped antibodies; and, (ii) a "small, inexpensive, trial-sized" antibody, created only inside lymph nodes, when B cells are creating new candidate antibodies in response to a newly-presented antigen sequence (those extra-small "testing" versions do not leave a lymph node, and are eliminated once a T cell chooses a "winning" B cell and signals it to begin making the full-sized versions). And, a rare type of antibody is called IgD, because it has a "delta" chain. Anyone who wants more info on (or pictures of) any of those can find that info easily, in Wikipedia or via an internet search.

So, that leave two main types of antibodies which actively help fight off pathogens and diseases. The easiest way to grasp a huge and crucially important difference between them, is to realize that:

(i) the "famous" type, usually called IgG ("immunoglobulin Gamma"), which essentially all educated people already know about, have shapes that roughly resemble the letter Y, because they have two "sticky arm" components, attached to a single "stem" component. Here are two ways to illustrate an IgG antibody:



ILLUSTRATIONS OF Y-SHAPED IgG ANTIBODIES, WHICH CAN ONLY FUNCTION INTERNALLY. THE TWO UPPER COMPONENTS CAN BE CALLED "STICKY ARMS", OR Fv ("fragment variable"), OR Fab ("fragment antigen-binding"). THE "STEM" COMPONENT WAS INITIALLY CALLED Fc ("fragment constant"), BUT WHEN SCIENTISTS REALIZED IT CHANGES SHAPE INTO A SIGNALING MODE, WHEN THE ANTIBODY BINDS TO A PARTICLE, THEY CHANGED THE Fc NAME TO "fragment crystallizable" (TO KEEP THE SAME Fc LABEL)

These Y-shaped antibodies can work effectively, ***only INSIDE the body***, because they do not carry any toxins, or defensive weapons, and they are much too small (as a single molecule) to be able to seriously entangle, slow down, or hinder even a virus, let alone a bacterial cell. So, they function by changing the shapes of their "stem portions", when either of the two "sticky arms" binds to something that looks dangerous.

We call that process a "***tag and flag***" process; the antibody effectively tells an apparent pathogen, "*Aha! I found you, and now I've caught you! And so,* ***TAG!*** *You are now* ***IT!***" The sticky arm(s) of the IgG will latch onto the particle, and when the stem

portion of that antibody changes shape, it effectively becomes a “flag”, attached to that particle, which begins the process of alerting the immune system that an invading foreign particle has been identified, latched onto by an antibody, and marked.

Next, a special class of proteins (called “complement proteins”) will recognize and bind to a “shape-shifted” stem on an internal IgG antibody. That binding reaction will trigger an “activation cascade” which will cause the complement proteins to have a “protective cap portion” removed, to expose an active portion. When complement proteins become “activated” – by binding to an IgG antibody which has bound to something – they perform the equivalent of attaching a loud siren and a flashing light to the shape-shifted stem of an IgG antibody. Any nearby immune cells will recognize and respond to those signals, and they will go to where the shape-shifted antibody, and the complement proteins, have attached to the alien/hostile/non-self/intruding particle.

However, in “secreted mucosal fluids” which are completely outside of any cells or tissues (those fluids include saliva, nasal mucus, digestive juices, lung fluids, fluids in the vaginal cavity and urethra, and fluids that keep the eyes lubricated), there simply are not enough immune cells (or complement proteins) present, in those fluids, to be able to offer any significant help, to any “shape-shifted” antibodies.

Therefore, in a beautiful, brilliant, and elegant feat of evolution, the immune systems of vertebrates somehow figured out (or “evolved with”) a way to strap two antibodies to each other, via their stem components, to create elongated antibody “dimers”, with each “dimer” containing two Y-shaped antibodies coupled to each other, so that each and every dimer contains not just two, but four “sticky arms” (with two at each end of a double-length molecule). Those dimers are called “secreted IgA antibodies” (or related phrases, such as “sIgA dimers”). Here is an illustration of an IgA dimer:



IgA “DIMERS” ARE FORMED BY ATTACHING TWO Y-SHAPED ANTIBODIES TO A PEPTIDE CALLED A “J CHAIN” (SHOWN IN GRAY), INSIDE A “B CELL” WHICH MAKES ALL THREE COMPONENTS. THAT “LIGHTLY ATTACHED” DIMER IS SECRETED BY THE B CELL, THEN IT IS PULLED IN BY A RECEPTOR PROTEIN ON THE BOTTOM (“BASAL SURFACE”) OF AN EPITHELIAL CELL. PART OF THAT RECEPTOR (SHOWN IN ORANGE) WRAPS AROUND THE STEM COMPONENTS AND J CHAIN, TO CREATE A STRONGER DIMER, WHICH IS THEN SECRETED BY THAT EPITHELIAL CELL INTO SALIVA OR MUCUS. THE “DOUBLE-STICKY DIMER” THEN PERFORMS A “GRAB AND DRAG” PROCESS, ON PATHOGENS.

Since a “tag ang flag” function is useless, in secreted mucosal fluids with no immune cells around, the **MUCOSAL** immune system developed a “grab and drag” process instead. If even a single sticky arm segment can latch onto some foreign particle,

the antibody will effectively block and prevent that particle from burrowing, tunneling, or otherwise penetrating into any mucosal cells or membranes. Instead, the IgA antibody will forcibly drag that particle down into the stomach acids (which will kill nearly all microbes), if they connected inside the mouth or nasal cavity; or, the antibody will keep that particle suspended in the liquefied and then semi-solid mass of food that is passing through the intestines, until the particle and the antibody get "pooped out" and eliminated from the body; or, if they connected inside the windpipe, bronchial tubes, or lungs, they will be coughed up, and either spit out, or swallowed.

Most people have never even heard of "secreted mucosal antibody dimers", and they have no idea that they even exist. However, here is an absolutely crucial fact, which can help people better understand how important they are:

In just the 3 to 5 pounds of secreted mucosal fluids that a typical human adult is carrying, at any given moment, there are MORE THAN TWICE AS MANY SECRETED IgA ANTIBODIES, THAN ALL OF THE Y-SHAPED IgG ANTIBODIES IN THE ENTIRE REMAINING BULK AND WEIGHT, OF THAT PERSON.

In summary, because of the factors described in Topic 1, the number of pathogens that infect animals by penetrating into a "mucosal membrane" is hundreds of times larger and more populous than the second-largest category of pathogens (i.e., "blood-borne" pathogens, usually transmitted by insect bites). So, driven by constant and pressing needs, mammals developed a specialized "mucosal" immune system, which operates in ways that are almost entirely separate from, and independent of, the internal immune system. The immune system figured out how to create IgA antibody *DIMERS*, and how to secrete them into the mucosal fluids that are no longer inside any cells or tissues (for anyone interested in more details about *HOW* they are made and secreted, in ways that go deeper than the figure caption above, download the patent application section available from this website, and search for the words "J chain" or "secretory component"). Then, once those sIgA antibody dimers have been created and secreted, they are entirely on their own, and they will get no more help from any other immune cells or components.

However, there are two unhappy and difficult facts, about ***injected*** vaccines, which everyone should know about.

The first unhappy fact is that injected vaccines do ***NOT*** trigger ***mucosal*** antibody formation, except perhaps as rare, sporadic, and unreliable side effects. As described on the next page, there simply has not been any good way, before now, to create vaccines that can safely and reliably trigger ***mucosal*** antibody responses, against any antigen sequences that are "loaded onto" those vaccine particles.

The second unhappy fact is this: in order to make ***injected*** vaccines more potent and effective, the complete injectable formulations must include harsh and unpleasant chemical additives, called "adjuvants". The reason why adjuvants must be "necessarily

nasty" compounds, used to intentionally irritate and inflame the muscle cells and tissues at the site of an injection, is described on the next page. And, it is hoped and believed that the "MALT-targeting" approach to creating mucosal vaccines can entirely bypass, and eliminate, any need to include any harsh, inflammatory adjuvants in the final formulations. If that can be accomplished, it will provide a major and much-appreciated step forward, to a point where MALT-targeting vaccines might earn and deserve the label of "Post-Adjuvant Vaccines".

[NEXT PAGE]

TOPIC 5. WHAT ARE "VACCINE ADJUVANTS"? HOW DO THEY WORK? ARE THEY INTENTIONALLY INFLAMMATORY, AND IRRITATING? ON BALANCE, ARE THEY GOOD, OR BAD? HOW AND WHY DO "MALT-TARGETING" VACCINES AVOID ANY NEED FOR ADJUVANTS? IS IT REALISTIC TO HOPE FOR "POST-ADJUVANT VACCINES"?

As a general definition, "adjuvants" are things that are added to vaccine formulations, to make them more effective and potent; and, to clarify that definition, they generally must rise above the level of being mere "excipients" (i.e., the types of pharmaceutical additives, such as diluting, liquefying, anti-caking, preservative, or other agents that help make the active ingredients of a drug function better), and must rise to a level that experts refer to as "immuno-stimulatory". And, anyone interested in this topic also should realize that there are a number of "gray areas" (or grey areas, in Britain), where it isn't clear whether some particular compound should be regarded as a mere excipient, or as an actual adjuvant. As an example, if a topical mucosal vaccine contains an agent called a "muco-adherent", which will cause vaccine particles in that formulation to cling more tightly (and/or for a longer period of time) to a mucous membrane, that agent might be called either an adjuvant, or an excipient; and, various phrases like "adjuvant-like activity" also are used, to deal with those types of "gray areas".

However, rather than becoming entangled in or distracted by those "gray areas", a clear focus needs to be placed on a very unpleasant truth, which lurks behind the "immuno-stimulatory" label that is commonly used to describe and defend adjuvants.

That highly unpleasant fact is this: essentially all adjuvants that are added to injected vaccines are, in truth, **deliberately and intentionally irritating, inflammatory, distress-causing additives**. Stated in other words, they are harsh, unpleasant, and "necessarily nasty" chemicals. Why? Because of a reason that no one has been able to overcome, or avoid, or eliminate, before now. Their goal, their role, their job, and their assigned task, is to rapidly and seriously irritate the muscle cells, at the site of an injection. Why? So that those distressed muscle cells will rapidly begin sending out distress signals (in the form of messenger molecules called "cytokines"), which will attract and recruit mobile immune cells to hustle over, as quickly as possible, to the site of the injection, so that the immune cells will be able to encounter, and begin processing,

the vaccine particles, as quickly as possible, before those particles (and the antigen sequences they are carrying) can be seriously diluted, diffused, degraded, or simply "pulled inside" by the normal cell and tissue repair processes at the site where the vaccine was injected.

A very substantial part of the widespread opposition to vaccines, and of the unwillingness of quite a few people to get vaccinated, probably arises from the unpleasantness of the adjuvants which must be added to injected vaccines, in order to protect as many people as possible, whenever a large population is inoculated. Although it is impossible to reliably tell, by asking people to respond to survey questions, our startup company would be willing to wager several thousand dollars, on a bet that the numbers and percentages of people who refuse to get vaccinated against conventional diseases (such as influenza, pneumonia, etc.) likely would drop by about 30%, and possibly more, if the mode of inoculation where to change from: (i) having to make an appointment at a pharmacy, and stopping whatever else you're doing, to go in and get a needle jabbed into your arm, knowing your arm is going to be sore and achy, for at least two days after you get that shot, to (ii) having a friendly cheer-leader type of person passing around a bowl of lollipops to a crowd that has gathered, partly for the vaccines, but also to see a band, comedian, school play, or church service. Therefore, in addition to the other benefits that we believe are likely to be achieved, as described **HERE**, if "MALT-targeting peptides" can indeed create "precision-guided vaccines", we also suggest that "higher rates of use, leading to reduced costs of caring for people who got sick because they did not get vaccinated" are yet another benefit that anyone reading this should at least consider, as a possible and even likely outcome. Indeed, if "MALT-targeting" vaccines can eliminate any need to inject harsh, nasty, inflammatory "adjuvants" into people, that result may come to be so widely welcomed and appreciated that these vaccines might come to be called "*Post-Adjuvant* Vaccines."

So, in answer to the question posed above – "On balance, are adjuvants good? Or, are they bad?" – the best answer would seem to be, "Well, they were good, when (and because) they were necessary, to help protect more animals and more people, against diseases. However, if and when they become no longer necessary, because of some scientific and medical discovery or advance that offers a *BETTER* way to reach that good result, then they will move into the 'Bad, on balance' category."

[NEXT PAGE]

TOPIC 6. (A) THERE ARE MORE THAN TWICE AS MANY *SECRETED MUCOSAL ANTIBODIES*, IN JUST A FEW POUNDS OF MUCOSAL FLUIDS IN A HEALTHY ADULT, THAN ALL OF THE *INTERNAL ANTIBODIES* IN THE ENTIRE REMAINING WEIGHT AND BULK OF THAT PERSON. THAT IS A POWERFUL INDICATOR THAT MUCOSAL ANTIBODIES ARE VERY,

VERY IMPORTANT, IN FIGHTING MUCOSAL PATHOGENS. (B) HOWEVER, BEFORE NOW, THERE WERE NO RELIABLE, NON-TOXIC WAYS TO USE VACCINES TO GET THE MUCOSAL PORTION OF AN IMMUNE SYSTEM, TO CREATE SECRETED MUCOSAL ANTIBODIES. (C) MALT-TARGETING VACCINES APPEAR TO BE FULLY CAPABLE OF CHANGING THAT, IN WAYS THAT WILL CREATE NOT JUST ONE, OR TWO, BUT ***FOUR MAJOR ADVANCES*** IN VACCINES

The previous pages in this website describe a number of specific points which now need to be assembled into a larger, cohesive structure or system:

(1) Nearly all pathogens have evolved in ways that enable them to attack and invade mucosal membranes, and they are (by far) the most important and numerous class of pathogens on this planet;

(2) The internal immune system simply is not designed, equipped, or suited, to deal with pathogens that can reproduce – usually, very rapidly – entirely within a single cell on the outermost surface layer of a mucous membrane;

(3) Therefore, to help fight off such pathogens, vertebrate animals evolved with ***mucosal*** immune systems that function independently of the ***internal*** defenses, and use ***secreted mucosal IgA antibody dimers*** which are very different from internal IgG antibodies, in both shape and function;

(4) There are more than twice as many mucosal antibodies, in just the few pounds of secreted mucosal fluids in a healthy adult, than all of the internal antibodies in the entire remaining weight and bulk of that person; and,

(5) The huge number of secreted mucosal antibodies is powerful and even compelling evidence that mucosal antibodies are hugely important, and valuable, in fighting off mucosal pathogens.

All five of those points directly support an even compel a hard conclusion: if any types of vaccines could trigger the creation of good and effective ***secreted mucosal antibodies***, those vaccines (and the antibodies they would help create) could be very useful, and helpful, against numerous different types of pathogens – especially pathogens that attack the "upper respiratory tract" (such as influenza, COVID, and "common cold" viruses). Indeed, that is not just an opinion. That hard fact has been known for not just years, but decades, and uncountable numbers of immunologists, vaccine companies, research groups at medical schools, government employees, and other, all around the world, have been trying their best, for decades, to create good – or "even just slightly better" – mucosal vaccines.

However, the sad and troubling fact is that, under the "prior art" (i.e., before the scientific community becomes aware of "MALT-targeting" vaccines), there are almost no

"really good" mucosal vaccines; and, there is almost no research currently being done on mucosal vaccines, because the only types of "adjuvants" which can make them work potently, in test animals, are too dangerous, and too toxic, to allow the results of any such research to be transferred over, to possible use in humans.

Here are five facts that can help illustrate and explain the limited and inadequate status of mucosal vaccines, prior to any announcements about MALT-targeting vaccines.

1. Even though there are hundreds (or thousands, depending on how different strains and variants are classified) of different mucosal pathogens, a recent review article dedicated entirely to mucosal vaccines (Rhee et al, "Mucosal vaccine adjuvants update," *Clin Exp Vaccine Res 1*: 50-63 (2012)) listed all of the commercially available human mucosal vaccines that the authors could find information about. However, that listing took less than a single paragraph, and it didn't even merit a table, to list them.

2. The so-called "FluMist" vaccine, which is administered via a nasal spray, usually reaches only about 30 to 40% efficacy, each year. Those numbers mean that 60 to 70% of the people who get that vaccine, still become infected by serious cases of influenza, each year, despite being vaccinated by it.

3. The most recent attempt to create a new nasally-delivered vaccine occurred in Switzerland, where a mucosal influenza vaccine was put into human use. However, even though it had performed well in animal tests, it ended up causing some of the human recipients to suffer a neurologic affliction called "Bell's palsy," which creates a partial paralysis of the facial muscles, usually on either the left or the right side of the face. As such, it can lead to strange, unsettling, sometimes bizarre, and in some cases grotesque and genuinely frightening facial expressions, among sufferers. That vaccine had to be withdrawn from the market when those cases began to appear, and the manufacturer was driven out of business, by the costs of the liabilities it was facing. That event is well and widely known, among vaccine experts, and it powerfully discourages any companies or researchers that might otherwise be tempted to launch an expensive research project into any other potential mucosal vaccine, no matter how promising it might be.

4. It appears that ***the only mucosal vaccine which has actually been commercialized for human use, since the year 2000***, is an orally-ingested vaccine against "rotaviruses" (which create severe digestive problems among infants, in tropical regions). However, the first attempt to release that vaccine led to major problems, and that first version had to be withdrawn, after it began causing a severe and potentially fatal intestinal problem called "intussusception" – which must be corrected surgically, as quickly as possible – in some of the infants who received that vaccine. The sponsoring company re-designed and re-tooled that vaccine, by reducing the number of rotavirus antigens the virus particles carried (which presumably made it somewhat less effective). It is now being sold under the trademark ROTA-TEQ (TM). So, to reach a better understanding of how limited mucosal vaccines have been, and are, and remain, to this day, ponder the fact that, ***over the last 26 years*** – despite all the progress that has been made, in every other branch of medicine – there has been only a sole, single new type of mucosal vaccine, that has become available for human use. And, it was for a tropical

disease that almost no one outside the tropics has ever heard of. And, it created severe (and severely expensive) problems, when it was first released; so, it had to be "retooled", to make it "tolerable" (and less effective).

5. Finally, one should ponder this fact: ***almost no one has ever even heard about mucosal antibody dimers,*** *EVEN THOUGH THERE ARE MORE THAN TWICE AS MANY OF THEM, THAN Y-SHAPED INTERNAL ANTIBODIES*. Why is that? Perhaps – just perhaps – the physicians and immunologists who know about them, do not like and do not want to talk about them, or call attention to them, because they have been unable to create any class of vaccines, or any approach to designing and making vaccines, which can reliably trigger the formation of mucosal antibodies, without having to use adjuvants that are so toxic that they would never be approved for any human use. It's human nature for people to *NOT* want to talk about things they are *NOT* good at; instead, anyone who must work for a living, and who needs support and income from other people, would prefer to focus on, and have other people know about, the things they *ARE* good at. So, the fact that almost no one has ever even heard of mucosal antibody dimers, is probably a fair indicator of how well vaccine researchers and companies have done, in their efforts to create vaccines that can trigger formation of those antibodies . . . which is to say, "Not very well."

More information to support and explain the facts listed above (and which further discusses the severe inadequacies of currently-available mucosal vaccines) is contained in the "Background Section" of a pending (not yet published) patent application, which can be downloaded via a button at the bottom of the Home page.

Accordingly, mucosal vaccines simply are not being actively and successfully developed, for human use, except by a few small startup companies, none of which appear to be taking the approach we are taking; and, vaccines which are injected almost never lead to mucosal antibody formation. That has created a huge and unmet need, for better methods for creating, not just vaccines that can be APPLIED topically to mucous membranes, but which will actively trigger the formation of secreted mucosal antibodies, when applied in that manner.

A summary of not just one or two, but ***FOUR major advances*** and advantages that we believe "MALT-targeting precision-guided vaccines" will be able to provide, can be found near the bottom of the page **HERE**.

[NEXT PAGE]

TOPIC 7. WHAT ARE PHAGES, AND "PHAGE LIBRARIES"? AND, HOW ARE "SCREENING TESTS" USED TO IDENTIFY AND ISOLATE THE "WINNING PHAGES" IN A COMPETITION?

This topic (and the next page) are included, to reassure any vaccine companies – or researchers who might be interested in MALT-targeting mucosal vaccines – that we did the work described herein, and that this isn't some effort to defraud or swindle anyone. It requires, first, a brief summary of phages, and what they are (and, that requires a bit of history). That is followed by a summary of what "phage display libraries" are, and of how "screening tests" can be thought-up, and used, to identify which particular phage particles, out of millions of "candidate" or "contestant" particles, happen to be carrying a foreign insert peptide which will cause those particular particles to be treated and processed in some particular way, by some particular type of cell, or tissue type, or animal.

That is "starting-point" information, to get someone ready to understand what is on the next page. That page describes the specific screening test we created, and used, to identify those particular phages (from among a billion candidates/contestants) which happened to be carrying foreign insert peptides which triggered and drove both M cells, and "immature dendritic cells", in MALT patches, to "determine" that those particular phages were so dangerous, and so important, that they would cause a full-scale antibody-forming response to start up and move into action, as quickly as possible.

WHAT ARE "BACTERIOPHAGES" (WHICH ARE NOW CALLED JUST "PHAGES")?

As a very brief introduction to "phages":

1. People had been experimenting for hundreds of years with various types of lenses, including "magnifying lenses", when the Dutch fabric merchant Van Leeuwenhoek became interested in trying to make them better, in the 1670s, so that he could more closely examine the thinnest, tiniest threads in the fabrics he handled. Once he got started, he kept refining and improving his magnifying lenses, until he could clearly see (in samples of water, rather than fabrics) microbes that actively moved, which people initially called "animalcules".

2. Within a few decades, after seeing and categorizing numerous types of bacteria and other microbial cells, scientists realized that there was an entire category of microbes that were infective, somehow, but which were too small to be seen by even the best light microscopes of that era. Those came to be called "viruses", after the Greek root word for "virulent". Until the 1930s, when electron microscopes were invented and scientists could actually "see" and begin to seriously study viruses, no one knew what viruses were, or how they could reproduce.

3. In the 1890s, a British scientist realized that there was some type of "virus", in some of the rivers in India, which could kill and inactivate the bacteria which caused cholera; and not long afterward, a different scientist discovered a similar "virus" that could kill and inactivate the bacteria which caused dysentery. Since cholera and dysentery were two of the worst scourges of armies, those findings quickly gained

attention, and when World War I began, several countries developed liquid drinks carrying those viruses, which they fed to their troops, to "immunize" those troops against cholera and dysentery (and, not surprisingly, counterfeiters selling nothing more than dirty water soon followed).

4. As scientists began looking for and finding other viruses that could attack and destroy other types of bacteria that caused other diseases, they realized that each such virus could attack only a very specific and limited class of bacteria. So, they named that entire category of viruses "bacteriophages", from the Greek root "phage", which translates into "aggressive eating", comparable to "devour" (as opposed to just "nibbling"). Later, "bacteriophages" was shortened to just "phages".

5. The noun "phage" has come to refer to any virus which: (i) can infect only some limited group, type, or class of bacterial cells; and, (ii) is classified as "non-pathogenic", and not dangerous, since phages cannot infect plants or animals, in any way. The search for new and additional types of phages became active and motivated in the early 1900s, because "phage therapy" grew into a major and crucial branch of medicine, before the advent of sulfa drugs and then penicillin. If someone was infected by a bacterial pathogen, the scientists and physicians of that era could usually figure out what type of bacteria it was, and they would administer, directly to the infected site, a batch of phages which could kill that type of bacteria. That approach has recently come back into favor, to help fight certain types of antibiotic-resistant bacteria.

PHAGE LIBRARIES (aka PHAGE DISPLAY LIBRARIES)

In the 1970s and 1980s, a group of scientists (led by Prof. George Smith, at the University of Missouri, who later won a Nobel Prize for that work) began developing new and clever ways to work with a specific class of phages called "*Inoviridae*" (aka *Inoviruses*). They are phages with extremely small genomes, which infect *E. coli* cells, and which have "filamentous" shapes that enable them to wriggle out of pores they create in *E. coli* cell membranes, without killing their host cells (which greatly reduces the number of fragments from dead cells, and makes *Inovirus* phages easy to purify and use). They also go through a double-stranded "replicative phase", which enables them to be handled and treated just like plasmids. And, they form the "capsids" (or shells, sleeves, etc.) which enclose their single-stranded DNA, by simply continuing to add more and more of the small brick-like "coat protein 8" (cp8) proteins to a capsid that is being formed, until the "tail end" of the DNA strand reaches the assembly site; that is also highly useful, since it allows exceptionally long foreign inserts to be added to *Inovirus* phages.

All of those useful and helpful factors were combined, in *Inovirus* phages, and that is why Smith and his research team selected *Inovirus* phages as their starting point, and raw material, when they began trying to figure out how to create "phage display libraries". The word "display" initially indicated that the foreign peptide inserts were

openly displayed on the surfaces of the phage particles; however, that soon became the standard and accepted format, and the word "display" slid down to optional status; so, now, these libraries are also simply called "phage libraries".

Summarized briefly, Smith and his team (and other research groups that later became involved, and contributed additional useful methods) figured out how to insert a short DNA segment, created by "random chemical synthesis," into a single specific site, in the genomes of *Inovirus* phages, in a way that would cause the altered DNA strand to encode and create engineered proteins which are carrying a small additional segment of also-random amino acids. The most popular and widely used phage libraries sold today carry a set of 12 amino acids as a "foreign insert", added to the outer tips of the long cp3 proteins, which function like the tentacles of squids that are hunting for food in the deep ocean, where there is no light. Each phage particle has 5 copies of the cp3 proteins, but all five copies are encoded by a single cp3 gene, so all five tentacle-like cp3 proteins, on any specific phage particle, will have identical copies of the foreign insert peptide which happens to be carried by that particular phage particle.

The work required to create really good phage libraries took decades; but, now that that work has been completed, and now that companies can make them quickly and efficiently, using computer-controlled machines, anyone can buy a phage library with about a trillion different "candidate" particles, all in a single small tube, for less than $1000 (e.g., www.neb.com, catalog number E8210S, which is a "kit" that also includes monoclonal antibodies and magnetic beads).

WHAT ARE "SCREENING TESTS", AND HOW ARE THEY USED?

The "trick" to using any phage display library comes in thinking up some new and useful type of "screening test", which will somehow identify which particular phages – out of millions of candidates/contestants in a small "aliquot" (i.e., a quantity of liquid having a known and specific volume, which will contain some known number or portion of the molecules or particles, taken from a larger batch of that liquid) – will be taken in and processed, in some particular way that is of interest, when all of the particles in that aliquot are treated in a certain way. Almost all "screening tests" will create some type of "fair competition" between the particles, such as by contacting all of the candidate/ contestant particles with a specific type of cell or tissue, and seeing which particles are pulled inside those cells (or, as alternate examples, by passing an aliquot of particles through an "affinity column" or other device; or, by infusing or injecting them into a lab animal, and then looking to see which ones reach some particular targeted cell or tissue type).

The basic rule of "screening tests" is that no one can predict, in advance, which particular particles will be able to do "the XYZ trick". So, if a scientist hopes to isolate and identify those few particles which can perform "the XYZ trick," s/he will need to figure out two things: (i) how to pit millions of phages against each other, as "candidates"

or “contestants” in a fair competition; and, (ii) what type of isolation or purification process the scientist can use, to identify (and, usually, to isolate, preferably in a still viable and reproductive form) those specific phages which happened to be carrying a foreign insert which enabled them to become “the winners” in that competition.

So . . . now that that starting-point information has been explained, the next page will describe the specific steps, and the specific screening tests, that were created and used to identify those few phages which happened to be carrying randomly-generated foreign peptide inserts that can function as potent “MALT-targeting” peptide sequences.

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TOPIC 8. THE SCREENING TEST WE USED – TO IDENTIFY AND ISOLATE DENDRITIC CELLS WHICH HAD COMMITTED TO BECOMING ANTIGEN-PRESENTING CELLS (i.e., THEY HAD MOVED THEIR CCR7 RECEPTORS TO THEIR OUTER SURFACES) – CHALLENGED MUCOSAL CELLS (FROM MALT PATCHES CONTACTED BY CANDIDATE PHAGES) TO SQUEEZE THROUGH 5-MICRON PORES IN A FILTER, TO GET TO HIGHER CONCENTRATIONS OF CCL19 (i.e., THE CHEMO-ATTRACTANT WHICH, IN NATURE, LEADS ANTIGEN-PRESENTING CELLS TO GERMINAL CENTERS IN LYMPH NODES)

As described on the first two pages of this website, the following factors shaped and guided the design of the screening test we created and used, to screen millions of “candidate/contestant” particles from a phage library, to identify those few particles which happened to be carrying randomly-generated peptide sequences which can be used to create better, more potent, faster-acting mucosal vaccines:

FACTOR 1: Our goal was to find a way to identify and isolate those few phages which were carrying (randomly-generated) foreign insert peptides, which could drive rapid uptake and processing by M cells and dendritic cells in the surface-mounted mucosal lymph nodes called MALT patches;

FACTOR 2: We learned/realized that a major cellular change occurs, when an “immature” (or pre-committed) dendritic cell transforms/activates/matures into a “mobile antigen-presenting cell”. That change moves CCR7 proteins from inside the cell, to the outer surfaces of the cell, where they can be contacted by a chemo-attractant (CCL19) which will lead that cell to a “germinal center” inside a lymph node, where T and B cells will be waiting for an antigen delivery.

Therefore, we figured out how to create a physical obstacle, in the form of a filter with pores that were small enough to enable an activated dendritic cell to squeeze through, but only if it was "motivated" to do so.

Here is a condensed summary of how we performed the screening test:

STEP 1: Tiny droplets (containing 20 million phages from a phage library, for each mouse) were slowly "infused" (i.e., via a micro-pipette, rather than injected via a needle) into the nostrils of each (sedated) mouse, in multiple different mice;

STEP 2: We waited 90 minutes, to allow the droplets and phages to slowly travel through the nasal airways in the snout of the mouse, and to give the M cells and dendritic cells enough time to perform all five of the steps described **HERE**, but not enough time for the dendritic cells to digest and break apart the phages they had pulled in;

STEP 3: The mouse was anesthetized, then sacrificed. To slow down cellular activity and prevent activated dendritic cells from breaking apart the phages that had triggered their activation, ice-cold saline was forcibly injected into the aorta, and emerged from the vena cava. As an alternative faster approach, the head can be severed quickly, then placed in a refrigerator (or a freezer, for about 10-15 seconds, then moved to a refrigerator).

STEP 4: A "skull section" was created, which exposed the MALT patches in the nasal airways (which are in known locations, in mice and rats). Using a stereo-microscope, a very thin brush was used, with gentle pressure, to harvest surface and near-surface cells from the MALT patch locations.

STEP 5. The harvested phage-exposed mucosal cells were loaded into the top chamber of a dual-chamber vertical tube device, which had been custom-assembled from a sawed-off segment of a plastic pipette having a diameter that allowed the tube segment to be lowered, vertically, into a well on a 48-well ELISA plate. The bottom chamber (i.e., the bottom of the well on the plate) contained a supply of the CCL19 chemo-attractant, and enough liquid to rise above a horizontal filter disk, described below, to allow molecules of CCL19 to diffuse upward, through the filter, into the upper chamber containing the mucosal cells. The top and bottom chambers were separated from each other by a filter having pores with 5-micron diameters, which had been glued into place using a rubber ring as a gasket, to render the top chamber watertight (the bottom chamber did not need to be watertight).

Most animal cells have diameters of roughly 10 microns, and dendritic cells are even larger. However, they evolved with an ability to squeeze through the gaps between neighboring cells in soft tissues, in ways similar to the "pseudopod" travel of amoebas, or to how an octopus can squeeze through a small opening, to get to a crab or fish. Therefore, the only cells that were both *ABLE . . . AND, MOTIVATED . . .* to squeeze through the 5-micron pores in the filter, were dendritic cells which had already moved

their CCR7 receptor proteins to their outer surfaces, by the time they were loaded into the separation tube.

STEP 6: The harvested phage-exposed cells were given two hours (at body temperature), to give any activated/transformed dendritic cells time to squeeze through the filter. The separation tube was then lifted out and discarded, and any cells that had reached the bottom chamber were broken apart, by a detergent that breaks apart cell membranes, but not phages enclosed within proteins. When the cells were broken open, whatever they released was plated onto a "lawn" of fresh host bacteria cells, on an agar plate.

STEP 7: Within two days, a few phage colonies began to appear, and "clonal isolates" from each colony was transferred into a fresh batch of host cells, in broth. When enough new "clonal" phages (i.e., all descended from a single ancestor, and having the same genetic content) had reproduced, the phages were purified, and a DNA preparation was made from each clonal isolate. The "foreign insert" sequences were "amplified", by polymerase chain reaction (PCR), and those DNA preparations were shipped to a DNA sequencing lab.

The resulting DNA sequences revealed what the amino acid sequences were, in the phages that had "won" the competition created by the screening test. Those were the phages which were carrying randomly-generated "foreign insert peptides" which had functioned – successfully and effectively – as "MALT-targeting *HYPER*-pathogen peptides", which had been able to initiate, and then drive all the way to completion, not just one or two cellular responses, but an entire series of five different and distinct cellular responses, by two different types of immune cells, leading to an irrevocable commitment, by a previously immature dendritic cell, to become an antigen-presenting cell.

Additional comments:

1. The amino acid sequences of the CCL19 chemo-attractant protein vary, between different species, but those sequences, for all animal types that are likely to be useful in research (including mice, rats, ferrets, dogs, cats, pigs, monkeys, chimps, ducks, and humans) are known, and can be readily located via Medline searches and gene databases. In addition, various versions (including from mice, rats, and humans) are readily available for purchase.

2. Anyone who looks into the CCL19 chemo-attractant cytokine will be likely to also see references to CCL21, which can perform in similar ways. We're not experts on the distinctions between those two molecules, but it appears (and we assume and believe) that: (i) CCL21 has other, additional effects (such as on T cells) which would not be helpful in the screening test we used; and, (ii) it does not appear that both CCL19 >> AND << CCL21 need to be present (as co-factors or similar agents), to get CCL19 to work. Therefore, we ignored CCL21, and only used CCL19. If any experts believe that

assumption and decision was incorrect or incomplete, they are requested to contact us.

3. As described on the "Plans & Goals" page of this website (see the button in the footer), we do *NOT* hope, want, or intend to ever become a manufacturing company, or to assemble the types of safety facilities and super-high expertise that would allow us to perform things like "pathogen challenge tests". Instead, our goal is to become a licensing company, and to work and cooperate with dozens of animal vaccine companies, to help them create and sell hundreds of different vaccines, for dozens of different animal types. Accordingly, we hereby offer to provide detailed step-by-step instructions (with reagent names and concentrations, incubation times and temperatures, and all other details) for how to perform these types of screening tests, to any vaccine company or research group that has the facilities needed to perform these types of tests. So, any company or research group that qualifies is invited to contact us, via the last page in this website.

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WHAT ARE OUR PLANS, AND GOALS? WHAT ARE WE HOPING FOR, FROM VACCINE COMPANIES AND/OR RESEARCHERS THAT HEAR ABOUT OUR WORK?

Rather than "playing our cards close to our chest", we would prefer that every vaccine company, research group, and government agency know exactly what we are doing, why we are doing it that way, what we hope to do next, and what they can expect from us in the coming months.

That approach makes the most sense to us, in light of the following factors:

- We do NOT have any facilities, or expertise – or any desire, at any level – to begin testing actual pathogens, in any types of animals. Instead, all of the work we performed directly was in a "startup incubator lab," which only allowed mice and rats to be tested, and which did not allow any actual pathogens to be tested, used, or brought into the labs; and, we aren't even renting that lab space any more, since the remaining work needs to be done in different types of facilities.

- We have absolutely no desire to ever become a company which manufactures or sells any type of vaccine. Instead, we hope to become a licensing company, and a company that promotes and enables as much research as possible, as quickly as possible, into as many types of mucosal vaccines as possible, for as many different types of animals as possible. And, those goals and desires are indeed affected by, and consistent with, a set of entirely humanitarian, altruistic, and benevolent hopes

and wishes. We want this technology to begin helping people find ways to minimize or completely avoid sickness, suffering, and disease, among animals as well as humans, and we want to do all we can, to help reduce and control healthcare costs.

- Although it is not a pressing goal at the moment, we also hope to eventually help lay a foundation for better, more useful, and more productive exchanges, between anti-vaxxers, and the scientific and medical communities. If these new types of mucosal vaccines can eliminate any need for the harsh and nasty adjuvants that injectable vaccines require, and can provide other important advantages as well, they may end up creating a "middle ground" where people on both sides of the pro-vax and anti-vax arguments can meet, and talk, and actually communicate with each other, rather than pointing fingers, making accusations, and trying to defend against and deny anything and everything "the other side" is doing, to "try to score points".

So . . . instead of wanting to compete against anyone, we hope to become a licensing company, which can:

- create a structure and system that will incentivize those who are already experts – in testing vaccines against actual pathogens, in one or more types of animals – to do those types of tests. How can we offer that encouragement and incentive? By both: (a) offering custom-engineered MALT-targeting T7 phage constructs, at low cost (we hereby commit to a $4000 price, for *each of the first ten* phage constructs, and we'll see what happens, after that), carrying ***any antigen sequence that a qualified requester will commit to actually testing, in "pathogen challenge tests", in one or more types of animals***; and, (b) openly offering a worldwide exclusive license, to *any and all use of our MALT-targeting delivery system, for any and all vaccines against a specific pathogen or disease, in one or more types of animals*, to the first animal vaccine company, vet school research group, or other qualified group which generates "proof of efficacy" that is sufficiently solid and detailed to enable "registration" (i.e., authorization for sale for use in animals) by the U.S. Department of Agriculture, for the requesting company to sell that type of vaccine. As a more detailed statement of that approach, the next page contains a single-page handout we provided to any interested visitors, at the World Vaccine Congress 2026, held in Washington DC on March 30-April 2, 2026.

- create an advisory board – if the research in animal vaccines looks strong and promising – to begin evaluating suggestions and proposals from vaccine manufacturers, for how they would suggest moving forward to begin testing and making MALT-targeting ***human*** vaccines against various diseases. In other words, we don't want to get ahead of ourselves, and we have made no decisions or commitments, of any sort, concerning human vaccines. Instead, if the animal work looks promising, we will begin talking with experienced people who have worked

in or with the human vaccine industry, to get their advice, and possibly their support and/or participation; and,

- begin talking with an organization called RADVAC, about whether and how some early small-scale clinical trials might be organized for doctors, nurses, and other health care workers, since they: (i) are highly and heavily exposed to new strains, mutants, and variants of both COVID and influenza, because of their work with infected patients; and, (ii) are in a position to make well-informed personal decisions, about whether they might wish to try and help test a mucosal vaccine against some new variant or mutant strain of either COVID or influenza, if that vaccine has been shown to create "neutralizing antibodies" of the "secreted mucosal IgA dimer" type, against some new and dangerous new strain of either type of virus. The RADVAC organization was formed in Boston by top-level biochemistry experts connected to Harvard and/or MIT (and, that work was funded mainly by internet billionaires with political attitudes that leaned in generally libertarian or at least highly pragmatic directions) soon after the COVID pandemic broke out in 2020, when the government announced that it might take up to two years before any effective COVID vaccines would become available. Those experts began working together to create the best oral vaccine they could create, to protect themselves and their loved ones, while waiting (or, "rather than merely waiting, passively") for government-approved vaccines. So, they are worth talking with, to see what they learned from those efforts and experiences. And, if people who actively work in health care (and who are frequently exposed to infected patients) can be shown enough hard, solid, trustworthy data – focusing on both mucosal antibody formation, and apparent safety – to persuade and convince *THEM* that the types of mucosal vaccines described herein can probably help protect people who are being actively exposed to infected patients, then it's hard to see why others should try to stop experienced and educated "health-care professionals" from doing what they can, to protect themselves, and their families and friends.

Stated in alternate words, we hope and intend to create a large number of licensing opportunities, for a substantial number of animal vaccine companies, in ways that (we hope) will end up creating a network of friends, allies, and partners, rather than creating enemies, adversaries, and opponents.

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IF YOU WOULD LIKE TO CONTACT US . . .

Please use this form to contact us, if you wish to open a line of communication between us. Tell us whatever you would like us to know (preferably, including the

company, agency, university, or whoever/whatever you work for or with, or, at least some sort of background info about yourself).

If you send us a text via this page, feel free to include 1 or more links to web pages, but do *NOT* try to attach any documents, pictures, videos, or anything else, to your initial text message. Please understand that if we visit any links you designate, we will do so on an old backup computer, and if we encounter any malware on your link, we can wipe that computer clean and restore it, with no difficulties; and, we will post whatever we can find out about you, and your attempted malware, on various boards, to warn good people to avoid you.

Before you send a message, please at least try to understand, and accept, that we cannot be pushed or shoved into either a pro-vax, or anti-vax, category. Instead, our only goal is *BETTER* vaccines. If you are opposed to vaccines, and if you chose to not read anything else on this website, then please, at least read the page about "adjuvants", which is HERE. In total sincerity, we are trying to help *EVERYONE*, by *ELIMINATING* the types of *inflammatory, toxic, and nasty adjuvant compounds* that are necessary, to make *injected* vaccines work properly, today.

And, beyond that potentially major advantage, we also hope to show companies and researchers how they can make new types of vaccines which can provide *BETTER* protection against literally hundreds of different mucosal pathogens, than any currently available vaccines. How? By triggering the formation of *BOTH OF TWO ENTIRELY DIFFERENT* types of antibodies: (1) the standard Y-shaped internal antibodies that injectable vaccines can create (we can do it without requiring any injections, or nasty adjuvants); *AND*, (2) by *ALSO* triggering the creation and secretion of mucosal antibody *DIMERS*, as well (which work by a totally different mechanism, and which *INJECTED* vaccines can*NOT* create, as described HERE).

THE "CONTACT US" TOOLS WILL NOT WORK IN THIS PDF FILE. THEY CAN BE FOUND – AND USED – AT www.pgvax.com/contact-us