

Cancer mRNA Vaccines as a Promising Approach for Treating Luminal A Breast Cancer

Alexandra Giuliani

International School of Monaco, 12 Quai Antoine 1er, Monaco, Monaco, 98000, Monaco; alexandra.giuliani@yahoo.com

ABSTRACT: Luminal A breast cancer is the most common subtype of the most common cancer in women. Current treatments using surgery and chemotherapy have greatly improved patient outcomes in recent decades but are still far from perfect. mRNA vaccines, which instruct the body to create specific proteins, hold the best promise going forward as a “cure” for luminal A breast cancer. Immunological therapies are emerging in solving problems that chemotherapy, surgery and targeted therapies cannot. The ultimate goal of immunotherapy would be to help the immune system recognize and destroy tumor cells as well as make antigens. In this paper, mRNA's potential for addressing the heterogenous nature of tumors, envisioning how it might be made to effectively elicit an immune response are explored; in particular, how it can be modified quickly to change which mutated genes it targets. This paper also discusses the limitations of this emerging technology and the difficulties of evaluating its efficacy when it has yet to enter clinical trials. Finally, this paper concludes by offering thoughts on how its development might be accelerated, predictions on effective targets, and likely dates for such a vaccine to debut as a real-world treatment.

KEYWORDS: Biomedical and Health Sciences; Cellular and Molecular Biology; Cell, Organ and Systems; Immunology; Cellular Immunology; Oncology; Breast cancer; mRNA.

■ Introduction

Breast cancer is the most common type of cancer in women besides skin cancer and the second most common cause of death after lung cancer. Worldwide, there are about 1.7 million cases of breast cancer diagnosed every year, with approximately one new case detected every 18 seconds.¹ It is estimated that 281,550 women in the US will be diagnosed with invasive breast cancer and 49,240 women will be diagnosed with non-invasive breast cancer this year.² There are several factors that may raise a woman's risk of developing breast cancer such as increasing age; personal history of breast cancer; family history of breast cancer; nongenetic, Nonmodifiable Risk Factors like race, early menarche /late menopause, etc.; and Modifiable Risk Factors like hormone use, tobacco, alcohol, and nutrition.³

Breast cancer begins when the healthy cells in the breast grow out of control and form a mass or sheet of cells called a tumor. Mutations affect the function of tumor-suppressor genes and/or oncogenes. The ‘multiple hit model’ of cancer formation hypothesizes that a single cell must have several damaged genes and receive a series of mutations that build up over time in order to become cancerous. This model shows why cancer is so hard to treat: these multiple genes mutate and interweave to create a complex and heterogeneous population of tumor cells.⁴ In a sense, one tumor can be considered multiple diseases. This is why scientists are trying to harness the immune system to fight cancer—it is the best possible defender against such a varied onslaught. Tumor suppressor genes can slow down cell division, repair damaged DNA and make cells go into apoptosis (programmed cell death). Cancer can be formed when these tumor suppressor genes do not work properly, causing the cells to grow out of control.⁵ Proto-oncogenes aid with cell growth; however, when these

genes mutate/change or overproduce copies, they can become permanently activated, from (proto-oncogene to oncogene) when they are not supposed to be. This causes the cell to grow out of control, leading to cancer.⁶

In this paper the breast cancer subtype Luminal A, also known as HR+/HER2- will be the focus. It is the most common subtype, making up 68% of all breast cancers.⁷ Hormone receptor (HR) positive means that the tumor cells have receptors for the hormones estrogen or progesterone, leading to the development of HR+ tumors. Human epidermal growth factor receptor 2 negative (HER2-) means that the tumor cells do not have abnormal levels of HER2 proteins.⁸

Prognosis for luminal type A is better than other breast cancer subtypes since it has high hormone receptor expression, negative HER2 expression (does not grow fast and is not likely to spread to the lymph nodes quickly) and a low proliferation rate (slowly dividing cells).⁶ While these factors give those with this cancer a better prognosis than most, it is notable that this subtype is the most commonly diagnosed. This combination of factors makes it a good candidate for testing experimental treatments to demonstrate the efficacy of new cancer technology. Treatment for breast cancer represents a great strain on the resources of public health, so essentially eliminating it would act as a boon to the system with cascading benefits for everyone.

Current Treatments for Luminal A Breast Cancer and Their Shortcomings:

Treatment decisions for breast cancer rely on immunohistochemistry markers as well as nodal status, tumor grade, and tumor size. Depending on these factors, one or a combination of these three treatment routes will be decided upon:

Surgery:

Early-stage breast cancers are often easily treatable with surgery, but undetected and large tumors progressing to later stages quickly become more difficult to treat this way.⁹ (This is because of the difficulty inherently involved in determining whether all cancer cells of large tumors have been successfully removed) Surgery is performed to remove as much cancer as possible. A mastectomy is a type of surgery where the entire breast or both breasts (double mastectomy) are removed. In contrast, a lumpectomy/breast-conserving surgery is one in which only the specific part of the breast with cancer is removed. An advantage of this type of surgery is that a woman can keep most of her breast, though she will often need radiation therapy as well. For early-stage breast cancer, breast-conserving surgery with adjuvant radiotherapy works best. Navigating the timeline (immediately, 6 months after, etc.).⁹ of and complications around reconstructive surgery adds an additional element of difficulty with this treatment pathway.

Chemotherapy:

Chemotherapy controls the cancer by restraining its spread, making it grow more slowly and killing cancer cells that may have metastasized (When the cancer has spread from one part of the body to another, presenting further complications to treatment that must move beyond the localized). Neoadjuvant chemotherapy (before surgery) might be given to patients to shrink the tumor so that it may be removed with less extensive surgery. Usually used to treat locally advanced cancer, neoadjuvant chemo can lower the risk of recurrent cancer. Adjuvant chemotherapy (after surgery) is given to kill cancer cells that were not removed in surgery or that might have spread and cannot be seen. This also lowers the chance of recurrent cancer. Chemo is often most effective if combinations of drugs are used: anthracyclines such as Adriamycin and Ellence can be utilized alongside taxanes such as Taxol and Taxotere for both adjuvant and neoadjuvant chemo, while more aggressive anthracyclines like Doxorubicin, pegylated liposomal doxorubicin, and Epirubicin are combined with taxanes like Abraxane to treat metastasized breast cancer. Side effects of these drugs include menstrual changes and fertility issues, heart damage, nerve damage (neuropathy), hand-foot syndrome, chemo brain, and fatigue.¹⁰

When looking specifically at luminal A and how it reacts with chemo, studies fail to show benefit for patients. It still remains to be determined if chemotherapy has clinical significance, especially for patients with positive lymph nodes—meaning that the cancer has spread from the original tumor to the surrounding areas but has not metastasized yet. One review compared 5-year survival-rate differences among patients with Luminal A tumors who received and did not receive chemotherapy: the rate for patients at high clinical risk and low genomic risk without distant metastases who received chemotherapy was 1.5% higher, while the absolute difference among patients at low clinical risk and high genomic risk was only 0.8% higher.¹¹ As nearly all luminal A-like tumors fall within the low genomic risk

category, these results demonstrate little benefit of adjuvant chemotherapy with this cancer subtype. Additionally, studies have shown that high-risk premenopausal patients with other breast cancer subtypes had beneficial results from receiving chemotherapy, while Luminal A patients did not experience such gains. Patients may even be harmed by the toxicities of the chemotherapy.

Targeted Therapies:

The main shortcoming of targeted therapies is that they are still very early in development. They rely on administering drugs specific to the patient's cancer subtype, generally in combination with other treatments, to perform actions like tumor shrinkage.¹²

For decades, endocrine therapy (fulvestrant-FASLODEX, letrozole-FEMARA) has been the cornerstone for management of luminal breast cancer. Despite the substantial benefit derived by patients from endocrine therapy, primary and secondary resistance to endocrine therapy are serious clinical issues.¹³

Pathways involved in the biology of endocrine resistance have been well studied in the last two decades, leading to the development of several classes of targeted agents that have been approved. Today, in the advanced setting, three distinct classes of targeted agents are approved for use: mTOR (everolimus-AFINITOR), CDK 4/6 (palbociclib-IBRANCE, ribociclib-KISQALI, abemaciclib-VERZENIOS) and PI3K inhibitors (alpelisib-PIQRAY).¹⁴

CDK 4/6 inhibitors are the most important of these, having changed the natural history of this disease in the advanced setting and being currently under study in the early setting.¹⁵ In short, combining endocrine and targeted therapies has changed the landscape in advanced disease; in early disease, it is possible to have a similarly large impact, particularly in patients with higher risk of relapse. Moreover, experimental targeted drugs are in development such as AKT/PTEN inhibitors (Ipatasertib and capivasertib).¹⁶

Efforts to develop new agents with SERD (Selective Estrogen Receptor Degradar) properties with potent antiestrogenic activity in breast tissue have led to the discovery and characterization of second and third generation SERDs, orally bioavailable, some of which are now undergoing clinical evaluation. These include Elacestrant, SAR439859, GDC-0810 and AZD9496, among others.¹⁷

Finally, it is noteworthy that the development of targeted-agent combinations for luminal disease faces several challenges. Firstly, outcomes are already exceedingly good for most patients. Additionally, late recurrences—after five years—are a possibility for at least 20 years, which translates into a very long period of follow-up looking for events to occur. Lastly, side effects of treatment considered acceptable in advanced disease, such as alopecia, may not be tolerated by patients with early disease.¹⁸

The Potential of mRNA Vaccines for Treating Luminal A Breast Cancer:

While there are many potential new treatments being explored for cancer, such as CRISPR gene-editing, microbiome treatments, and cell therapy, the one that holds the most promise

ise for luminal A breast cancer in particular is mRNA vaccine technology. There are a few types of vaccines being explored as potential cancer treatments: immune cell-based vaccines, peptide-based vaccines, viral vector-vaccines and nucleic acid-based vaccines. (At least one vaccine, inoculating teenagers against the human papillomavirus, is currently working to reduce future rates of cervical, anal, oropharyngeal, etc. cancers that are caused or contributed to by the virus.)¹⁹ mRNA vaccines in particular are classified as nucleic acid-based and hold an especial potential to protect against infectious diseases and rapid malignant cell growth.

mRNA is, in essence, a template of instructions for how to build a protein. This technology has been gaining promise as the coronavirus pandemic has brought a lot of attention to it. The two most prominent COVID-19 vaccines in the US both utilize mRNA, which has skyrocketed interest (and funding) for additional mRNA research.²⁰ Both BioNTech and Moderna are pursuing mRNA cancer vaccines.²¹ These prove to be a little trickier than an mRNA vaccine for a virus since that case deals with clearly foreign viral matter, while cancer vaccines have to train the body to identify those portions of itself that are “foreign” malignant cells.²²

How will this work? A particular sequence of mRNA will be injected into the muscle and taken up by any cells in the surrounding area. The immune system will then hopefully recognize the proteins coded for by the mRNA as foreign and mount an immune response. The result of the immune response is that if the antigens are immunogenic enough, the T-cells (white blood cells that actively seek out the cancer cells and destroy them) will learn how to recognize these cancer cell antigens as foreign. This chain of events should trigger an immune response, wherein B cells (which produce antibodies that protect us from getting infected if, for instance, a virus enters the body) will subsequently seek out similar tumor cells.²³

mRNA-based cancer vaccines can target tumor-associated antigens, expressed in cancerous cells, for example, growth-associated factors, or choosing specific antigens that are unique to malignant cells owing to somatic mutation. These neoantigens provide tumor-specific targets for developing personalized cancer vaccines.²⁴

In short: upon administration of mRNA vaccines, tumor antigens will be expressed in a heterogeneous group of immune cells in order to help antigen-presenting cells activate and elicit an immune stimulation.

To ensure the mRNA reaches its destination, naked mRNA (after *in vitro* transcription, it is not bound to protein and vulnerable to different enzymes that are going to recognize it) can be formulated with a delivery vehicle (vehicle-loaded mRNA).²⁵ Delivery vehicles help to improve stability, RNA uptake and translatability of mRNA vaccines. Application of exogenous RNA combined with a polymeric carrier was also shown to activate the immune system by generating a local immunostimulatory environment.²⁶

mRNA vaccines are a strong choice over other vaccines for treating cancer because they are potent, safe and easily (as well as inexpensively) modifiable. The production of mRNA

is simpler and easier than protein production and purification and results in a more stabilized product.²⁷ The trick is in trying to deliver the mRNA in a way that helps maximize potency while doing that safely. Potential methods for maximizing potency include modifications made to the structure of the mRNA molecule (e.g., self-amplifying mRNAs, codon optimizations, nucleotide modifications, etc.) and different means of formulation (lipid nanoparticles, peptides, polymers, etc.).²⁷ But again, a strength of working with mRNA is how readily its sequence can be changed to add or swap targeted antigens. The quickly swappable nature of mRNA vaccines is the best way to address the challenge presented by tumors’ high degree of heterogeneity.

While mRNA vaccines are providing a powerful new avenue for treating cancer, there do remain challenges to creating an effective mRNA cancer vaccine. The products are required to be the right purity of mRNA, sequenced as well as delivered and administered properly. Given the difficulty of determining what factors are specifically driving an individual’s cancer to be out of control, it is hard to pick the right protein to encode instructions for in the mRNA that will elicit the needed immune-system response. This goes alongside the general issue with cancer therapies of managing the differentiation of normal tissue from cancer cells.²⁷

That said, this work is not merely theoretical: mRNA vaccines are already being developed in the treatment of other cancers (such as skin, lung, and pancreatic cancers).²⁸ Several clinical trials with mRNA vaccines against cancer are ongoing, and nonclinical research is active in this field. Noteworthy results were released in November 2020 of an mRNA mixture being injected into mice with skin and lung cancer that successfully triggered an immune response. Cytokines produced by this response were able to shrink 85% of tumors in the mice in the span of 40 days.²⁹ These cancer vaccines, produced by the same companies behind the mRNA vaccines for COVID-19, will soon be entering clinical trials with humans in an exciting next step.

Possible Components of an mRNA Vaccine for Luminal A Breast Cancer:

In light of the above, a theoretical combination of treatments that will in effect “cure” luminal A breast cancer can be proposed. In particular, a way forward using mRNA vaccines that will effectively address the inherent heterogeneity of tumors that so often impedes traditional cancer treatments can be outlined.

From the outset, picking the right target is the biggest hurdle in making the mRNA vaccine against cancer. The first potential target would involve picking a protein present in the cancer cells but not the healthy ones—i.e., the genes that are most mutated. When looking at luminal A breast cancer, PI3KCA is the most mutated gene (about 45%), followed by MAP3K1, GATA3, TP53, CDH1, and MAP2K4.³⁰ Genes like PI3KCA contain instructions to make proteins such as the p110 alpha protein (p110- α , subunit of phosphatidylinositol 3-kinase). This gene encodes a lipid kinase involved in vital signaling pathways, fundamental for cellular functions (e.g., growth, death, and proliferation).

However, when PI3KCA is mutated, there is a change in the single amino acid produced in the p110- α , leading to the production of an altered p110- α subunit that in turn makes PI3K abnormally active. This allows PI3K to signal without regulation. The unregulated signaling results in uncontrolled proliferation of cells, causing cancer.³¹ Therefore, targeting the altered p110- α in this mRNA vaccine could successfully short-circuit this entire process.

To circumvent cancer resistance observed with chemotherapy and given the heterogeneity of tumors (not every cancer cell they are in will be equally vulnerable to the use of one targeted antigen), it would be better to use two or more mRNAs. As such, this vaccine could ideally deliver not one but several different mRNA sequences encoding for distinct proteins, ideally eliciting a robust immune response towards the full spectrum of what the cancer is expressing. However, a possible drawback here is the potential for creating a situation where there is an autoimmune response.²⁵ It is not desirable to encourage the immune system to attack more than just the cancer and damage healthy cells, and yet more targets inherently increases the chances for this to happen. To avoid this scenario, it may make sense to start with a single mRNA molecule and test for whether it creates a strong enough response; if it does not (as is likely), a combination of molecules would be used or one after the other could be used to see what works best. A combination of PI3KCA, MAP3K1, and GATA3 could work well, for instance, at which point it would be possible to pare down to fewer targets to determine which target or combination of targets made it so effective.

Direct administration of complex mRNA is now considered to be a fast and feasible approach. However, there are several problems with the mRNA vaccine such as limited *in vivo* delivery, possibly due to enzymatic degradation, and limited intracellular delivery due to the large size of the mRNA molecule compared to other payloads. This could be overcome by screening different delivery materials and formulation methods.

Another possible avenue of interest might be to combine mRNA vaccines with immune checkpoint inhibitors. Most tumors strive to evade the immune system by expressing immunosuppressive proteins on their surface, called checkpoint proteins. Immune checkpoint inhibitors work by blocking that checkpoint. This prevents the “off” signal from being sent, allowing the immune cells to kill cancer cells. For instance, high CD70 expression may inhibit the anti-tumor immune response and is a promoter in tumor progression.³² CD70 expression (how much protein there is) could allow the tumor cells not to trigger an immune response. By inhibiting immune response, the CD70 could work against the mRNA vaccine. As such, any ways to diminish that possibility (such as combining with different treatment options) should make this vaccine more effective.

■ Discussion

Only studies can truly determine the efficacy of new treatments, which limits the possibilities of what a literature review in this area can accomplish. And as few mRNA vaccines for

cancer treatment are yet in clinical trials, they are not widely reported on in the literature—making research into this area difficult. That said, the success of mRNA vaccines in fighting the spread of the novel coronavirus signals a clear turning point in this technology. The possibility of a groundbreaking treatment here should not be denied.

With the right antigen selection and fine-tuning of mRNA delivery, payload size, etc., it is possible to unlock the full potential of the best ally each human body always had in attacking cancer cells: the human immune system. If the immune system can be properly instructed to treat cancer cells as the “foreign” bodies that they essentially are, their eradication of luminal A breast cancer tissue could end up being far more complete than what is possible with surgery and chemotherapy alone—and in a way that improves patients’ physical and psychological outcomes as treatment becomes less invasive.

This ‘hacking’ of the immune system is a new and exciting field of science that is moving at a rapid clip. With how quickly mRNA vaccines can be developed, deployed, redeveloped, and redeployed, progress should be expected quickly. The promise of mRNA vaccines (and possibly oRNA and miRNA as well) as proposed above for luminal A breast cancer is not a far-off or far-flung dream, but a promise that will likely be realized within the next decade or two.

■ Conclusion

mRNA vaccines are a highly promising route for treating or even “curing” luminal A breast cancer. They should continue to be explored at an aggressive pace, with increased funding allotted to speed them into clinical trials in the wake of their massive success in combating COVID-19.

It is likely that, in order to effectively address the heterogeneity of tumors, these vaccines will have to target multiple antigens simultaneously. This paper predicts that PI3KCA and MAP3K1 will prove the most worthwhile genes to target, and that doing so with effective payload delivery and minimal autoimmune response triggered will be possible in real cancer therapies by 2035. Particular attention should be paid to how best to combine these mRNA vaccines with existing treatments like surgery and chemotherapy as well as other cutting-edge treatments like targeted therapies.

These advances in treatments should function as a “cure” for luminal A breast cancer by 2040, with the relieved burden on the health care system as well as on women everywhere ushering in a new age of wellness and positive life outcomes. Even more excitingly, given the flexibility with which researchers can rework mRNA in the lab, any advances in mRNA vaccines for cancer should prove a ready boon to cancer researchers of all stripes—and assuredly to those looking into other perennial diseases likewise.

■ Acknowledgements

Thank you for the guidance of Daniel Wilson, my mentor from Carnegie Mellon University, in the development of this research paper.

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■ Author

Alexandra Giuliani is a junior at the International School of Monaco. She enjoys studying molecular biology and looks forward to researching biotechnology in college.