CANCER VIROTHERAPY
RIGVIR®
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CANCER VIROTHERAPY
RIGVIR®

Antonio Jimenez, M.D.
Medical Director, Hope4Cancer Institute

Subrata Chakravarty, Ph.D.
Chief Scientific Officer, Hope4Cancer Institute
DUAL MECHANISM OF ACTION
With its “seek and destroy” homing mechanism that targets cancer cells and powerful immunomodulating influence, Rigvir represents the birth of a new paradigm in cancer therapy.

50+ YEARS OF HISTORY
New treatment, but backed by over 50 years of committed research and leadership.

BACKED BY ROBUST CLINICAL DATA
Clinical studies on about 2000 patients demonstrate quantitatively the effect of the treatment against several cancers.

SAFE, NON-TOXIC, NON-PATHOGENIC
The genetically unmodified virus has an impeccable safety record, high selectivity for cancer cells, and is non-toxic and non-pathogenic.
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**RIGVIR®: A NEW ERA IN CANCER TREATMENT**

**INTRODUCTION**

Hope4Cancer® Institute proudly introduces Rigvir®, the latest addition to our arsenal of treatments. Rigvir® is a registered cancer drug in Latvia that has passed safety and efficacy clinical trials. Developed over the course of the last 50 years, Rigvir® represents a paradigm shift in the treatment of cancer. Our partnership with the Latvian Virotherapy Center allows us to bring this affordable treatment to the medicine cabinets of cancer patients around the world.

**Why is Rigvir® Different?**

Rigvir® is the first live, genetically not modified, non-pathogenic virus, registered as a drug that specifically seeks and destroys cancer cells. Rigvir® differs from most cancer medicine that focuses on finding chemotherapeutic, surgical and radiation-based treatments to treat cancer, none of which meet the criteria of providing selective and effective long-term action against cancer, without having life disrupting side effects.

As is often the case with science, the annals of research hold unapplied treasures, waiting to be revealed. One such concept was cancer virotherapy, cancer cells’ sensitivity to viruses, a fact known since the early 1900s, but not exploited for decades.

Scientists in Latvia developed Rigvir®, the first virus capable of targeting cancer selectively without any side effects. As accredited partners of the Latvian Virotherapy Center, Hope4Cancer® Institute is proud to deliver Rigvir®, the next turning point in the world of cancer therapy.

Rigvir® is the first, not genetically modified, non-pathogenic live virus to be registered as a drug and used by oncologists. It uses a two-pronged mechanism of action against cancer: one, seeks and destroys cancer cells, and, two, modulates the immune system.

Rigvir® is well tolerated and has virtually no side effects.

Rigvir® has completed safety and efficacy clinical trials on almost 2000 cancer patients. It is prescribed by oncologists and stocked in pharmacies in Latvia.

Clinical tests have proven Rigvir®’s effectiveness against melanoma, stomach cancer, colorectal cancer, prostate cancer, pancreatic cancer, lung cancer, sarcomas, kidney cancer and uterine cancer. Rigvir® can be adapted to other cancers as well. Only institutions accredited by the Latvian Virotherapy Center with specifically trained physicians can prescribe Rigvir®.
Advantages of Rigvir®

Similar to chemotherapy and radiation, Rigvir® directly affects cancer cells as they undergo cytolysis (cell breakdown). That is where the similarity ends. Listed are some key advantages of Rigvir® Cancer Virotherapy that make it stand-out as the treatment of choice.

- Cancer virotherapy utilizes the property of oncotropism, where the virus “seeks” out the cancer cells selectively, inducing specific, cytotoxic immune mechanisms within them. Healthy cells remain unaffected.

- Cancer virotherapy has a very high therapeutic index, in some cases as high as 10,000:1 (meaning that 10,000 tumor cells breakdown for every affected healthy cell). Chemotherapy and radiation, however, operate within narrow therapeutic windows where effectiveness cannot be divorced from the toxic effects.

- Cancer virotherapy triggers immune response while chemotherapy and radiation suppress it. This results in the faster and more effective elimination of cell breakdown toxic materials, whereas in the case of chemo and radiation the toxicity persists and impacts quality of life and survival.

- Multiple courses of cancer virotherapy can induce tumor immunological regression that triggers apoptosis, or regulated cell death. This process is suppressed in cancers.

- Cancer virotherapy can be applied both to local tumors and metastasized (systemic) tumors.

- Cancer virotherapy can be used as a synergistic drug before and after radical surgery to prevent the onset of metastases.

- Cancer virotherapy is extremely important for the treatment of tumors that are insensitive to chemotherapy and radiotherapy.

- Cancer virotherapy when used in combination with other therapy methods in oncology (surgery, chemo, radiation, hormone therapy) decreases the immunosuppressive effect caused by these methods.

In the current state-of-the-art among known oncolytic viruses, Rigvir® is the first and only registered, genetically unmodified virus to possess not only tumor cell destroying properties, but also immune activating properties.

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In my 25 years of treating cancer patients, as well as researching and investigating new cancer treatments, I have never come across a treatment that has a product profile quite like that of Rigvir®. Rigvir® combines excellent efficacy, immune system activation and an unparalleled safety profile. This data is backed by clinical studies conducted over decades that conclusively prove the product’s efficacy against a variety of cancers including melanoma, prostate cancer, lung cancer, sarcomas, bladder cancer, uterine cancer and more. Cancer patients owe it to themselves to consider Rigvir® as their treatment of choice.”

- Antonio Jimenez, M.D., Medical Director, Hope4Cancer® Institute
Mechanism for viral oncolysis is pictured here. A virus (yellow) invades a cancer cell, replicates inside the cell and finally breaks down the cell (cytolysis), resulting in the escape of replicated viruses that can then invade other cancer cells.

The Discovery of Oncotropism and Oncolysis. The history of cancer virotherapy goes back to the early 1900s when vaccination of a viral agent in cancer patients was found to show an unexpected improvement in their condition. In the 1940s, scientists discovered that tumor cells showed increased sensitivity to viruses. It was found that viruses could proliferate selectively in animal tumors (oncotropism). In some cases, this behavior was accompanied by oncolysis (breakdown) of the cancer cell. This discovery demonstrated that viruses, at least theoretically, could be used as anticancer therapies. But there were still many roadblocks in the way of making cancer virotherapy a viable and practical therapeutic reality.

Evidence Accumulates. From the 1950s through the 1970s, more data was gathered. It was shown that measles induced temporary remission in patients with Hodgkin's disease and Burkin's lymphoma, oncolytic activity was observed for influenza viruses, enteroviruses and others. Successful reports exist of the use of adenoviruses in cases of cervical cancer and enteroviruses in gastrointestinal tumors.

Stumbling Blocks from Lab to Clinic. The thought of having a viral drug that can hone in on a tumor and destroy it was very attractive. However, some serious stumbling blocks got in the way of making that dream a reality. First, some of the patients who were given viral oncolytic drugs developed uncon-
trollable viral infection from the injected virus. Second, in most cases the purposeful viral “infection” was met with a strong immune response from the body that seriously attenuated the oncolytic effect. Third, some clinical trials failed to follow the appropriate ethical criteria, seriously undermining the credibility of viral oncolysis as a valid and legitimate opportunity against cancer.

A SHORT HISTORY OF RIGVIR®

Discovery of Oncolytic Enteroviruses. In 1960, scientists at the August Kirchenstein Institute of Microbiology and Virology found that viruses obtained from the intestines of healthy children were able to destroy malignant tumors. Enteroviruses became the focus of research. Among the viruses tested were Coxsackie A & B viruses and ECHO viruses. In 1965, a laboratory of cancer virotherapy, the very first laboratory of its kind, was established in Riga, Latvia, headed by Professor Aina Muceniece with the undertaking of studying enteroviruses and their application as virotherapy agents.

Clinical Trials and the Discovery of Rigvir®. In 1968, the first clinical trial focused on the oncolytic ECHO group viruses was started, which included stage IV patients who had failed conventional therapies. The objective of this initial trial was to find the optimal tolerated dose, determine the spectrum of cancers sensitive to the viruses as well as evaluate their epidemiological and clinical safety.

The ECHO-7 group virus was found to have the highest anticancer activity. Not only that, it was found to be non-pathogenic (i.e., it was unable to replicate in the normal human body), and epidemiologically safe. This virus was selected and adapted to melanoma cells and named Rigvir®, or the “Riga virus”, named after the city of its discovery.

Two decades later, a clinical study on Rigvir® was conducted at 3 Riga hospitals that continued over 24 years (1968 - 1992), testing Rigvir® for its anti-recurrence, anti-metastatic and immunomodulating properties, particularly in relation to melanoma patients. The trial included 819 cutaneous melanoma, 100 eye melanoma and 239 gastrointestinal tract cancer patients - mostly stage III and IV. These studies also compared Rigvir® to standard chemotherapy and radiotherapy with stellar results.

Rigvir®’s Approval as a Cancer Drug. Between the years 1990 - 1995, patients with a number of different cancers were treated with Rigvir® at the P. Stradins Clinic and Latvian Oncology Center. In 2002, Rigvir®’s patent was approved, and in 2004 it was registered in the State Agency of Medicines of the Republic of Latvia. Since 2008, Rigvir® has been available as a prescription medicine in pharmacies. In 2011, it was included in the list of state compensated medicines for patients with cutaneous (skin) melanoma.

Hope4Cancer® Receives Accreditation. In 2014, Hope4Cancer® received accreditation as a center authorized to treat cancer patients with Rigvir®, opening a new avenue for this treatment to reach cancer patients across the world. As a certified Rigvir® physician, Dr. Antonio
Comparing Rigvir® cancer virotherapy to standard chemotherapy or radiotherapy is similar to comparing the impact of a laser guided Tomahawk missile to that of an atomic bomb. The powerful selective, destructive action, when combined with the avoidance of collateral damage, give Rigvir® a place in cancer medicine that has, until now, remained unoccupied.”

- Subrata Chakravarty, Ph.D.
Chief Science Officer, Hope4Cancer® Institute
MECHANISM OF ACTION

Rigvir® is an Enterovirus. Rigvir® is an enterovirus that has some unique characteristics. Enteroviruses are resident in the gastrointestinal tract and are thus characterized by a strong resistance to the acidic environment prevalent in the stomach. They are resistant to many detergents and disinfectants and remain stable at room temperature for a long time.

Enteroviruses are present everywhere. Some of their species are pathogenic – such as the polio virus – while others are harmless. Rigvir® is part of the type that is characterized by its lack of pathogenicity.

The Infection Process. Most enteroviruses use different cell surface proteins as receptors and co-receptors. One such receptor is the CD55/DAF-3 factor, which is a regulator of the complement cascade. This binding assists the virus in penetrating the cancer cell membrane.

Rigvir®’s initial immunomodulating property can also be explained by its engagement of cell surface receptors. Cancer cells develop receptors such as CD55 and CD59 that help them avoid the complement attack from the host immune system. By blocking these receptors, Rigvir® restores immune response to these cells, making them visible to the body’s defense mechanism (see explanation on next page).

Once inside the cell, new virion particles are formed in the cytoplasm of the cell using the cytoplasmic RNA to decode the viral proteins and replicate the viral RNA.

Oncolytic Activity. The oncolytic activity of Rigvir® was enhanced by several passages through tumor cell lines. The tumor cells undergo degenerative-dystrophic changes (oncolysis) and form hypertrophied nuclei followed by intensive vacuolation of the cells. Signs of cell lysis appear 2-7 days after application of Rigvir® with some cells showing only bare nuclei. After repeated courses of Rigvir®, tumor cells start exhibiting apoptosis (programmed cell death). This is significant, because tumors develop a strong resistance to apoptosis, resulting in proliferation.

Immunomodulating Activity. In addition to its oncotropic and oncolytic properties, Rigvir® shows a profound immunomodulating activity. Rigvir® has been shown to activate the immune system at the level of the lymph nodes, lymphoid tissues as well as the immune cells. It stimulates humoral immunity which includes B cells, antibody production, induction of interferon simultaneously with activation of cellular T-system immunity processes. In peripheral blood, cytotoxic CD8+, CD38+, CD95+ and activated T cells are elevated along with apoptosis receptors. The images below show the activation of these pathways culminating in melanoma cells getting surrounded by recruited lymphocytes.

The primary goal of Rigvir® therapy is to encourage the immune system to ensure tumor rejection. The repeated courses of Rigvir® are designed to accomplish that goal - of preserving the active stimulation of the immune system.

It has been shown in real patient experiences that repeated application of Rigvir® results in gradual regression of lymph node micrometastasis and subcutaneous metastasis.

Melanoma Cell Changes Caused By Rigvir®. I. Melanoma cells before application of Rigvir®. II. Cells from the same patient after several courses of Rigvir® start showing apoptotic tumor cells, lymphocytes, and plasma cells. III. This image shows a melanoma cell surrounded by recruited lymphocytes after Rigvir® application. [Muceniece A, Venskus D. How to assess immunity - the melanoma model. 2007. p. 116-117].

CD55/DAF AND THE COMPLEMENT SYSTEM

One of the components of the body’s immune system is called the complement system. The complement system is an extremely complex set of more than 30 proteins either circulating in plasma or bound to cellular membranes. This system is best known for its role in the body’s innate immunity, protecting it from a variety of pathogens.

HOW DOES THE COMPLEMENT SYSTEM WORK?

In the healthy body, the complement proteins exist in the plasma in inactive forms (zymogens). However, during an infection, the complement proteins get activated, and react with one another, massively amplifying the effect of the first interaction with a pathogen.

The net results of the complement activation are:

a. They bind covalently to pathogens, opsonizing (marking) them for engulfment by phagocytes that have receptors for the complement.
b. They serve as chemoattractants to recruit more phagocytes to the site of infection as well as activate them.
c. They can damage the pathogenic cells by using the molecular cylinder-like end products of the cascade to create pores in the cell membranes. Fluid can enter through these pores causing the cells to swell and explode.

The complement system also causes leaky blood vessels and cells that result in inflammatory conditions.

THE ROLE OF THE COMPLEMENT SYSTEM IN CANCER.

For a long time, there was confusion about the role of the complement system in cancer. It was believed that the complement system was actually oncogenic, i.e. supported the development of neoplasms. The connection between inflammation and cancer on one end and the complement system on the other was cause to raise the red flag.

Today, it is understood that cancer cells learn how to inhibit the complement system thereby protecting themselves from immune attack. The

Pictorial representation of a cell membrane being punctured and lysed by complement proteins.

overexpression of cell surface proteins such as CD46, CD55, and CD59 can disable the complement amplification process in the early stages by releasing enzymes such as C3 convertases.

Rigvir® is suggested to bind and disable e.g. CD55/DAF-3 factor. This step restores immune response to cancer cells, making the cells vulnerable to complement system attack. In addition to that, Rigvir® uses its reversible attachment to the cell receptors to gain entry into the cell (oncoptropism). Using this dual mode of action, Rigvir® can lead cancer cells to their oncolytic destruction.

Pictorial representation of CD55/DAF-3 showing short consensus repeat (SCR) domain where Rigvir® is suggested to bind.
KNOWN CANCERS SENSITIVE TO RIGVIR®

COMMON MECHANISM OF ACTION AGAINST CANCER TYPES

Rigvir® has been tested extensively against a variety of cancers. The following cancers have been found to demonstrate sensitivity to the virus. The ability of Rigvir® to address different types of cancers can be attributed to the engagement of cell surface receptors by the virus that are common to a variety of cancer cell lines. For cancers not listed, patients can request an evaluation to ensure that Rigvir® is sensitive to their cancer type. Also, see Frequently Asked Questions section in the back.
PRE-CLINICAL RESEARCH & CLINICAL STUDIES
Studies on the oncolytic activity of the ECHO viruses began in 1960. After careful selection, optimization, and pre-clinical observations established their promise as a medicinal target, clinical trials on five attenuated ECHO viruses started in 1968 at the Kirchenstein Institute of Microbiology. In 1988, advanced clinical studies began on the selected candidate, Rigvir®, where its efficacy was compared to chemotherapy and radiotherapy.

This section outlines the preclinical studies on Rigvir® which include its oncolytic activity and animal toxicological and immunological safety studies.

**ONCOLYTIC REDUCTION OF CANCER CELL VIABILITY CAUSED BY RIGVIR®.** Rigvir® has been tested extensively against a variety of cancer cell lines. The figure below shows micrographs demonstrating the impact of Rigvir® on two melanoma cell lines within 24 hours of administration. The loss in cell populations is apparent, demonstrating the effectiveness of this therapy at the cellular level.

The images on the next page show the progression in oncolysis for cell cultures of a variety of other cancers. The top set of images shows the phase contrast and Giemsa stained micrographs for pancreatic cancer cell line HPAF-II, measured at 24 h and 48 h, following application of Rigvir®. The image at 48 hours shows a substantial decrease in cell population and oncolytic damage to the cells under the influence of Rigvir®.

Similar results are seen after 24 hours in other cancer cell lines including lung, stomach, tongue, and breast cancers as well as monocytic leukemia. The micrographs for stomach, colon, and tongue cancer, as well as rhabdomyosarcoma are shown here as well to illustrate the effect of Rigvir®.

**SAFETY STUDIES**

Rigvir® has been tested on laboratory animals and has been found to not affect their cardiovascular or central nervous systems. The test animals also did not demonstrate any allergic or local irritation reactions.

Immunological tests have been conducted as well. Rigvir® induced antibody-forming cells in the spleen (2-fold increase). It is also observed to raise hemaglutinin levels and stimulate late hypersensitivity reactions. A short-term depression in
macrophage activation is observed. The phagocytic index does not reduce, and the complement system activity is not compromised. Virus stimulating antibodies and melanoma associated antigen expression are also observed.

These data clearly demonstrated Rigvir®’s efficacy against a variety of cancers, while maintaining a high level of safety and tolerance. In most studies, oncolytic viruses have a therapeutic (effectiveness/toxicity) ratio of up to 10,000, giving the product a very large selectivity window that far exceeds that demonstrated by conventional chemotherapy and radiotherapy methods.
Clinical Study Groups. The research team in Riga conducted a series of clinical studies on Rigvir® to measure the safety and efficacy of the product in humans. The results clearly demonstrate the excellent safety profile of the product combined with survival efficacy in a clinical environment that paved the way for the use of Rigvir® in humans as a registered drug.

The breakdown of the main clinical trial groups is shown below. One set of clinical trials involved a total of 976 patients with different forms of cancer (other than melanoma), who were evaluated for safety of the product. Out of these, 196 patients who had stomach, rectal, colorectal, and lung cancer, were followed for survival.

Another group of 919 Rigvir® treated melanoma patients (out of which 100 had eye melanoma) were followed separately to study their survival over a period of 3 years.
Safety, Side Effects, and Quality of Life. A total of 976 patients were followed to determine the safety and side effect profile of Rigvir®. There was no untoward record of any side effects from the treatment or its discontinuation. The most common side effect noted was sub-febrile temperature.

In a therapeutic area where severe side effects are a norm and accepted readily by patients and caregivers as inevitable, Rigvir® presents a new paradigm in safety and efficacy which has resulted in a better quality of life for patients on the treatment.

Efficacy Against Gastrointestinal Tract Cancers. Patients with different forms of gastrointestinal cancers (stomach, colon and rectal) were followed for Rigvir® efficacy. The following observations were made (see Table 1):

- A group of 21 stage III stomach cancer patients using Rigvir® demonstrated a 2-fold improvement in their 5-year survival rates (from 24% to 48%).

- A group of 14 rectal cancer patients showed an improved 5-year survival rate of 71% compared to 58% for the control group.

- A second group of 60 Rigvir® patients with rectal cancer (stages II, III and IV) showed a 5-year survival rate of 78%, improved from a range of 41-68% for the control group of rectal cancer patients at the same stage of the disease.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Number of Patients</th>
<th>5-Year Percent Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rigvir®</td>
<td>Control</td>
</tr>
<tr>
<td>Stomach Stage III</td>
<td>21</td>
<td>48</td>
</tr>
<tr>
<td>Rectal</td>
<td>14</td>
<td>71</td>
</tr>
<tr>
<td>Rectal Stage II-IV</td>
<td>60</td>
<td>78</td>
</tr>
</tbody>
</table>

Table 1. 5-Year Survival With Rigvir® When Used On GI Tract Cancers

Efficacy Against Melanoma Patients. Patients with different forms of melanoma (cutaneous, eye, facial skin, oral mucosa) were followed for Rigvir® efficacy. The following observations were made (see Table 2):

<table>
<thead>
<tr>
<th>Melanoma (Stage)</th>
<th>Number of Patients</th>
<th>Percent Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rigvir®</td>
<td>Surgery Only</td>
</tr>
<tr>
<td>Cutaneous (Clark 2-5, Nx-1M0)</td>
<td>49</td>
<td>84</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>149</td>
<td>84*</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>156</td>
<td>78*</td>
</tr>
<tr>
<td>Cutaneous (T1-4N0,1M0)</td>
<td>25</td>
<td>84</td>
</tr>
<tr>
<td>Cutaneous (pT1-5N0,1)</td>
<td>252</td>
<td>78*</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>142</td>
<td>78*</td>
</tr>
<tr>
<td>Eye</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>Facial Skin, Oral Mucosa</td>
<td>46</td>
<td>57</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>919</td>
<td>80**</td>
</tr>
</tbody>
</table>

* P < 0.05.
‡Number of patients at stage I=7, II=20, III=12, IV=7.
*Not determined.
**Average percent survival across data sets (N.D. not included in averages).
Table 3. Efficacy of Rigvir® in Melanoma Compared to Other Immunotherapy (5-Year Survival) Based on Depth of Invasion.

<table>
<thead>
<tr>
<th>Depth of Invasion (Clark)</th>
<th>Number of Patients</th>
<th>Percent Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rigvir®</td>
<td>Alternate Therapy*</td>
</tr>
<tr>
<td>pT1-3</td>
<td>67</td>
<td>29</td>
</tr>
<tr>
<td>pT4-5</td>
<td>35</td>
<td>19</td>
</tr>
</tbody>
</table>

*immunotherapy treatment included C. parvum, Levamisol, Splenin.

Table 4. Efficacy of Rigvir® in Melanoma Compared to Other Immunotherapy (5-Year Survival) Comparing Cases With or Without Metastases in Lymph Nodes.

<table>
<thead>
<tr>
<th>Metastases in Lymph Nodes</th>
<th>Number of Patients</th>
<th>Percent Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rigvir®</td>
<td>Alternate Therapy*</td>
</tr>
<tr>
<td>Primary focus without metastases to lymph nodes</td>
<td>111</td>
<td>53</td>
</tr>
<tr>
<td>Primary focus with metastases to lymph nodes</td>
<td>20</td>
<td>14</td>
</tr>
</tbody>
</table>

*immunotherapy treatment included C. parvum, Levamisol, Splenin.

Efficacy Against Melanoma, Including Eye Melanoma. A series of clinical studies (summarized in Table 2) on a total of 919 patients shows that Rigvir® performed significantly better than treating the disease by surgical methods alone.

On the average, across the data sets, Rigvir® outperforms surgery by improving 3-year survival rates by 45%. In other words, 4 out 5 melanoma patients on Rigvir® survive for three years or more, when only about 1 out of every 2 patients who are treated by surgery alone managed to survive in the same time frame.

Out of every 10 patients with eye melanoma, 9 patients survive for 3 years or more.

One of the most challenging forms of melanoma involve often inoperable scenarios where the cancer spreads through the mucosa. Even in those cases, 57% patients on Rigvir® treatment were able to survive for 3 years or more.

Efficacy of Rigvir® Against Deeply Invasive Melanomas Compared to Other Immunotherapy. A 5-year survival study was conducted on 102 melanoma patients who received Rigvir® Virotherapy following excision of the primary tumor. Patients were divided into two groups based on the depth of invasion of the cancer (Table 3).

Once again, survival of Rigvir® treated patients outperformed those receiving other immunotherapy treatment (Corynebacterium parvum, Levamisol, Splenin). For melanoma spread to Clark pT1-3, a 15% improvement in 5-year survival.
was observed. When Rigvir® was used for melanoma patients where the cancer had spread deeper (Clark pT4-5), a more profound impact was observed with survival rates increasing by 82%.

**Efficacy of Rigvir® Against Melanomas Spread to Lymph Nodes Compared to Other Immunotherapy.** A similar study comparing Rigvir® with other immunotherapy agents was conducted on patients with and without metastases to the lymph nodes (Table 4). Following excision of the primary tumor, patients were treated with Rigvir® or with alternate immunotherapy (C. parvum, Levamisol, Splenin).

A profound effect was seen in patients with lymph node metastasis, showing 185% improvement in 5-year survival rates for those treated with Rigvir® compared to those receiving other immunotherapy agents.

**Post-Registration Experience in the Treatment of Melanoma Patients With Rigvir® Between 2005 to 2011.** The figure on top right shows a comparison chart of the Kaplan-Meier estimates for progression-free survival for 80 Stage II melanoma patients who have been divided into those receiving and not receiving Rigvir®. The period of time that they remain(ed) progression free was also recorded.

The chart clearly outlines the success of Rigvir® in improving survival rates over the 6-year window of observation.

Another chart (next page, top) shows that Rigvir® clearly assists in containing progression (and metastasis) in a group of stage II melanoma patients.

In this analysis, only 6 out of 44 (i.e. 13%) patients on Rigvir® showed progression. In the same time frame, 21 out of 36 (i.e. 58%) of the patients who were not in the Rigvir® group showed progression.

Since cancer adapts rapidly, often developing resistance against chemotherapy drugs and radiation, the ability to sustain therapeutic effect against cancer is a crucial element that makes a cancer therapy extremely attractive.

**Kaplan-Meier Estimates of Progression-Free Survival (Stage II Melanoma Patients).** Patients on Rigvir® treatment were compared to others to evaluate the ability of Rigvir® to minimize instances of recurrence and progression of disease.

The patient presented melanoma (T4 N2c M0, Breslow 15 mm, ulceration) that was diagnosed and excised in April 2004. Subsequently, the patient was treated with Roferon (Interferon-alpha) and subjected to five additional excisions conducted between January 2006 to September 2007.

In February 2008 (see images on next page, bottom half), the patient started Rigvir® treatment, which continued through April 2011. The image taken in April 2010 (below, to the right), when compared to the initial image on the left, is illustrative of the powerful benefits of Rigvir® for melanoma patients.
Rigvir® Drastically Reduces Cases of Progression of Disease in Stage II Melanoma Patients. A total of 44 stage II melanoma patients on Rigvir® were compared to others (control group). The control group showed much larger populations (21 out of 36) showing progression of disease within approximately 20 months. In comparison, only 6 out of 44 on Rigvir® showed progression.

Illustration of the Action of Rigvir® in a Case of Melanoma. The patient was tracked for a period of three years following the start of Rigvir® therapy in 2008.
Hope4Cancer® Institute is a clinic in Baja California, Mexico, known for its integrative approaches towards cancer therapy. The clinic avoids the use of treatments that cause toxicity and immune suppression. Using these methods, the clinic has obtained significant results in the treatment of cancer, especially with refractory cases that have failed chemotherapy and radiotherapy treatments.

Hope4Cancer® was founded in 2000 by Dr. Antonio Jimenez, M.D. Trained as a conventional doctor, Dr. Jimenez embraced integrative non-toxic approaches to cancer ever since he was able to cure his father’s Stage IV prostate cancer prognosis. With over 25 years of experience as a physician, Dr. Jimenez is also an avid clinical researcher, and has traveled the world looking for effective methods to treat cancer.

Recently, Dr. Jimenez traveled to Latvia on the invitation of the Latvian Virotherapy Center to obtain training in the use and administration of Rigvir®, a powerful new approach to treat cancer with a drug that did not demonstrate the negative side effects of chemotherapy and radiotherapy. After receiving the required training in Riga, Latvia, Dr. Jimenez is today a Rigvir® certified physician. In addition to that, Hope4Cancer® Institute has obtained accreditation from the Latvian Virotherapy Center as a center capable of administering Rigvir® to patients.

Hope4Cancer® Institute’s treatment approach includes the use of anticancer agents that use a variety of mechanisms of action in combination with principle-based complementary approaches that provide relief to the body by reducing the toxic burden, modulating the immune system, providing appropriate nutrition, oxygenation and microbial load.

The Rigvir® treatment protocol followed at Hope4Cancer® Institute will follow the standards set by the Latvian Virotherapy Center where Rigvir® is used as a standalone therapy.
Is Rigvir® a Vaccine?

We are often asked, “Is Rigvir® a cancer vaccine?” While Rigvir® and vaccines both use viruses or viral materials as vectors, they differ on some key points that are discussed below:

**Mechanism of Action: Multimodal vs. Unimodal.** Rigvir® uses multiple mechanisms to kill cancer cells, while vaccines are typically unimodal. In its first mechanism of action, Rigvir® infects cancer cells directly and breaks them down by oncolysis - cell death happens via a combination of apoptosis, necrosis, pyroptosis and autophagic cell death. Second, the impact of Rigvir® on weakening tumor vasculature affects the uninfected cells that die by apoptosis or necrosis. Finally, Rigvir® kills cancer cells by activating the body’s immune complement system and tumor-specific immune cells. The induction of the immune system also impacts cancer cells in nodules in the primary site and metastatic locations.

Vaccines work by one mechanism alone: the stimulation of the immune system against a specific target. **Standard vaccines** consist of weakened or dead microbes or part of microbes that are able to stimulate
the immune system against itself. They are weakened viruses to minimize the risk of infection. The activated immune system preserves a “memory” of the pathogen so that it is ready to respond in future infective events. In that sense, cancer vaccines are not true vaccines but are biological response modifiers that work to stimulate and/or restore the ability of the body to ward off the disease.

Cancer vaccines are of two types: Preventive (prophylactic) cancer vaccines target microbes that are known to cause cancers. For example, Gardasil® and Cervarix®, both approved by the U.S. Food and Drug Administration, protect the body against two types of human papillomavirus (HPV), known to cause approximately 70% of cervical cancers in the world. Another FDA approved vaccine protects the body against Hepatitis B Virus (HBV), known to cause liver cancer. Cancer therapeutic vaccines are designed to treat cancers that are already developed. Cancers are known for their ability to shield themselves from the immune system. A therapeutic vaccine must: a. be able to trigger an immune response against the specific cancer, and b. remove the mechanisms built into the cancer cells designed to evade even a fully functioning immune system. In practice, no effective therapeutic vaccines have been developed so far, since launching an immune response against a growing cancer that can mechanically avoid the immune system response has proven to be ineffective. Provenge® is the only FDA-approved cancer vaccine available today that has shown some results against prostate cancer.

While Rigvir® can launch an immune response, it combines that property with its ability to unmask the cancer cells, while at the same time, directly infecting the cell. These properties make Rigvir® a complete, targeted anticancer therapy.

Rigvir® specifically targets cancer cells and results in activation of the immune system. Risking the consumption of an immunosuppressive modality in an already immune suppressed disease condition is not a good strategy. Rigvir® ensures that the body’s immune system starts recognizing the cancer cells in local and distant metastatic focal points.

Vaccines are also known to block the lymphatic system with large foreign proteins which could lead to cancers such as leukemia and lymphoma.

Other potential side effects that are associated with specific vaccines include: shallow breathing connected with sleep apnea and SIDS (sudden infant death syndrome), multiple sclerosis, spinal cord inflammation, severe allergic reactions (HPV vaccine), intussusception (intestinal blockage) (Rotavirus vaccine).

**Immune System Suppression.** Vaccines suppress the immune system by taking away the opportunity, especially for children, to build up their natural immunity, that is induced in the body by fighting off infections. The artificial immunity generated by vaccines weakens the body’s immune response, leaving people more vulnerable to other infections.

**Difference in Side Effects.** In contrast with vaccines, Rigvir® demonstrates virtually no side effects. Vaccines, however, have been implicated with numerous side effects that implicate both the active ingredients as well as additives in the preparations.

Commonly used vaccines have the risk of rare but serious side effects such as anaphylactic shock, paralysis and sudden death. Vaccines can also trigger autoimmune disorders such as arthritis, multiple sclerosis, lupus, Guillain-Barre Syndrome (GBS), and other disorders. In addition to that, vaccines can cause brain inflammation (encephalopathy) which can lead to death or permanent brain damage and disorders such as autism, ADD/ADHD, and other developmental problems. Certain additives such as thimerosal (still present in some vaccines) has been associated specifically with the development of autism.

**Rigvir®’s Selective Toxicity and Ability to Modulate the Immune System** make it a highly attractive treatment choice compared to other conventional options. Other treatment options such as chemotherapy and vaccines compound their limited efficacy with toxic side effects and depression of the immune system, hurting the body’s ability to recover from the treatment, let alone the disease.
Is Rigvir® Just Another Type of Chemotherapy?

Chemotherapy is the use of chemical agents that have been shown through preclinical and clinical studies to be toxic to cancer cells. The chemicals used in chemotherapy are typically small molecules that can interfere in a number of ways with a cell - for example, covalently binding to nucleic acids (DNA, RNA), interfering with the DNA synthesis, enzymatic action - all resulting in the arrest of cellular growth and reproduction.

Rigvir® can be thought of as a biotechnology product that delivers a live virus with the capacity of specifically targeting cancer cells and modulating the immune system to recognize the cancerous cells. As an approved, oncological drug, Rigvir should not be confused with alternative medicine. Instead, it ranks as the first in a new class of conventional drugs.

Here are some of the key differences between the two treatment modalities:

Toxic Side Effects. Chemotherapy has a very small therapeutic window where the side effects of the drug quickly overcome the benefits of the treatment. Tolerance to side effects naturally depends on the severity and frequency. The toxicity of chemotherapy drugs is such that it can cause many documented side effects, including death, in significant percentages of patients receiving the therapy. Chemotherapy side effects include fatigue, pain, neurotoxicity, sores in mouth and throat, diarrhea, nausea and vomiting, appetite loss, constipation, blood disorders, loss of cognitive function, sexual and reproductive issues, hair loss etc.

Rigvir® has not shown any side effects other than sub-febrile fever and some fatigue.

Immune System Suppression. Chemotherapy (as well as radiation) cause immune suppression by paralyzing the bone marrow and decreasing the white blood cells, red blood cells and platelets. In severe cases, complete myelosuppression (destruction of bone marrow stem cells can also occur). Rigvir®, on the other hand, positively modulates the immune system.

Recurrence of Cancers. One of the biggest problems for patients treated with chemotherapy is recurrence of cancers - often resistant to chemotherapy. Recent research points to cancer stem cells that stay protected from chemotherapy and regrow into tumors with “intrinsic knowledge” about the chemotherapy agent. Rigvir® results in superior survival statistics for patients when applied with chemo and radiation, or surgery, than when the latter methods are used without Rigvir®, demonstrating its protective effect against recurrence.

Overall, Rigvir®’s precise selectivity and immunological properties lend to a superior therapeutic profile that cannot be rivaled by other existing conventional methods of treatment.

How is Rigvir® Stored?

Rigvir® must be stored at a temperature below -20 °C (-4 °F) at all times. Patients can transport the frozen product vials in an insulated container surrounded by dry ice. Most home freezers are capable of sustaining temperatures of -20 °C (-4 °F).

However, a home refrigerator is subject to temperature variations caused by frequent opening and closing and introduction of food products at higher temperatures. To avoid these issues, we recommend that patients invest in purchasing a small chest freezer that can sustain the needed temperatures (approximate cost US$300).

How Much Does Rigvir® Treatment Cost?

Many factors can influence the overall cost of the treatment including length of time as an in-patient, additional treatments, tests, and consultations, and length of Rigvir® treatment itself. The Admissions Team will be happy to discuss the specific costs of each patient’s treatment prior to signing their patient contract.

Given that oncolytic viruses have been known for over 50 years, why is it that it has taken so long for a drug in Rigvir®’s class to get approved?

Much of Rigvir®’s history is discussed in the chapter on Cancer Virotherapy. While the normal life cycle of a drug from discovery to approval in recent times is about 10-15 years, the research that it takes in developing the concept can precede the discovery by years or even decades. The approval of Rigvir® must be viewed in the context of the development of the field of oncolytic virotherapy as a whole. Every drug has a story, so does Rigvir®.
In the 1960s, many inspiring results added value to the concepts of oncotropism and oncolysis (ability to seek and destroy cancer cells) as the properties of certain viruses started gaining clear definition. However, the field of oncolytic virotherapy had some controversies to deal with on its way to gaining recognition, and it is only at the turn of the century that it started to get accepted as a serious approach to cancer therapy. Let us discuss why.

First, many potential treatments were developed from viruses with infective potential, e.g., the influenza virus. In other words, there was always the concern that patients could develop a viral infection from the treatment. Second, viruses can stimulate a virus-specific immune response from the body which can dilute the oncolytic potential of the therapy cells. Third, the multimodal mechanisms of action were very poorly understood, which affected implementation. Fourth, some clinical studies with oncolytic viruses conducted in the 1980s that did not follow ethical standards seriously undermined the potential of the therapy. Fifth, the failure of therapeutic cancer vaccines and the confusion of their similarity to oncolytic virotherapies influenced the recognition of oncolytic virotherapy as a treatment of an independent standing.

As a result the overall field was embraced with trepidation by the international research community for decades.

However, in the same timeframe, an oncology team at the August Kirchenstein Institute of Microbiology and Virology in Riga, Latvia (at that time, part of the Soviet Union) discovered that the ECHO-7 type of enterovirus showed all the qualities needed for a successful oncolytic virotherapy. The virus was proven to not cause infection, not replicate in any cells other than cancer cells and it did not stimulate a powerful immune system response that hampered the delivery of a significant viral “dose” to the cancer site. It was later understood that this virus could stimulate the immune complement system as well, unclaking the cancer cells to the body’s immune system. As the scientists embarked on the final clinical studies, the entire political scene changed and Latvia regained its independence.

By the mid-90s, extensive clinical studies had been completed and the efficacy and safety of Rigvir® was established. In 2004, the product was registered by the State Agency of Medicines of Latvia for administration as an oncology drug specifically against melanoma. Since then, research has continued, and Rigvir®’s clinically relevant oncolytic effect against a variety of other cancers continues to be discovered.

How Does Rigvir® Compare With Other Cancer Virotherapies?
What Is the Difference Between Genetically Modified and Unmodified Virotherapies?

Rigvir® is the first and only clinically approved, not genetically modified, non-pathogenic cancer virotherapy in the world. Protected by patents, Rigvir® has two extremely important qualities: one, the virus is not genetically modified, and, second, it is not pathogenic.

Many other well established pharmaceutical and small biotech sector companies are racing to develop cancer virotherapies, but all those products are based on genetically modified viruses. For example, Amgen has a product called Talimogene that is in Phase III clinical trials for melanoma. This genetically modified virus is based on the pathogenic Herpes simplex virus. To our knowledge, eight other companies are attempting to develop an oncolytic virotherapy based on genetically modified viruses.

Why is this important? Within our bodies, human cells are outnumbered by microbes in a ratio of 1:10. While microbes (including viruses) are better known for their pathogenic properties, they play an integral role in maintaining balance. The ability of viruses of affecting oncolytic damage specifically to cancer cells is an example of that natural process. To this day, none of the isolated, natural, unmodified viruses have been as capable of sustaining oncolytic and immunomodulating activity without pathogenic consequences as Rigvir. This has required pharma and biotech companies to look for genetic modifications, hence damaging the perfection of nature.

It is clear that Rigvir® has been able to capture a unique niche in the cancer virotherapy product spectrum. By harnessing the power of a live, non-pathogenic, naturally occurring virus, Rigvir® makes the best of nature’s exquisite complexity.
Does Rigvir® Work On Cancers Not Listed in This Document or as a Pure Immunotherapeutic Product?

Rigvir® is designed as a cancer virotherapy drug and claims can only be made against cancers that have undergone rigorous clinical tests in the facilities of the Latvian Virotherapy Center. It should be noted that Rigvir® is registered as an immunomodulator. Rigvir® can modulate the immune system by eliciting both an adaptive immune response and a complement system reactivation through a process that appears to be common for many cancers. This common mechanism of action may allow for uses that are much broader in impact than we currently know.

For patients, we recommend that they speak with the Admissions Team to determine their eligibility for Rigvir®.

Does Rigvir® Work With Chemotherapy, Radiation and/or Surgery?

Yes, it can. This question comes up often for patients who are already committed to a conventional treatment plan, but are aware of the limitations of chemotherapy, radiation and surgery as treatment methods and are looking to overcome them.

While Rigvir® is a standalone therapy in its own right, it has been shown to be a very powerful adjuvant therapy when used with other conventional measures. Rigvir® can be given before and after surgery and staged to be given alongside chemotherapy and radiation. Besides its synergistic oncolytic effect, Rigvir® assists in preventing metastatic spread. Most importantly, Rigvir® can reverse the immunosuppressive conditions caused by conventional therapies. Immunosuppression makes patients susceptible to other diseases, prone to cancer recurrence and greatly impacts quality of life during and after treatment.

Is Rigvir® Available in USA and Canada? How Can a Patient In These Countries Get Rigvir®?

Rigvir® has gone through a complete drug approval process in Latvia, but has not yet gone through regulatory approval in USA and Canada. However, Rigvir® is now available through the Hope4Cancer® Institute in Baja California, Mexico.

Hope4Cancer® Institute is the only approved center in the entire western hemisphere (including the Americas), accredited by the Latvian Virotherapy Center, where Rigvir® is available as a treatment for cancer patients. Mexico’s well developed medical tourism industry makes it easy for patients from USA, Canada and other countries to visit our clinic in Mexico for their treatment with this powerful, new therapy.

Do Patients Need to Visit Hope4Cancer® Institute for Rigvir® Treatment?

While Rigvir® is approved for ambulatory care (i.e., treatment outside of the hospital or clinic setting), we require most of our patients to receive in-patient care at Hope4Cancer® Institute for a period of approximately 3 weeks, following which the patients continue their treatment at home.

Patients with special circumstances should discuss details with our Admissions Team.

“As a Doctor Treating Cancer Patients, How Can I Prescribe Rigvir®?”

You cannot prescribe, but you can most definitely refer. Many physicians look for new and effective ways to help patients overcome the frustration of ineffective cancer therapies, or simply look for ways to synergize the good work that they have already done.

If you are one of them, please contact us to discuss ways in which you can refer patients to us for their treatment. We are happy to establish special, ongoing relationships with physicians who would like to work with us on an extended basis to strategize therapies for their patients.

Further Questions?

We look forward to answering any further questions you may have regarding Rigvir® and treatment for cancer at the Hope4Cancer® Institute. Please contact us by phone or email:

Phone:
1-888-544-5993 (USA Toll-Free)
+1-619-544-5993 (International)

Email:
info@hope4cancer.com
Rigvir® is delivered as an intramuscular injection (virus titre: $2 \times 10^6 - 2 \times 10^8$ CPD₅₀/ml, dosage = 2 ml).

Rigvir®’s API (active pharmaceutical ingredient) is the non-pathogenic ECHO-7 wild virus strain, adapted to melanoma cells (Picornaviridae genera, Enterovirus genus, ECHO group type 7).

The sequence difference from the wild virus strain Wallace is about 20%.

Virus strain is stable (tested for ca. 20 years).

Induces only rare side effects (temperature around 37.5 °C (99.5 °F) for 1-2 days and fatigue).

Does not contain antibiotics, stimulants, and other potentially toxic substances.

Must be stored at a temperature of -20 °C (-4 °F) and transported frozen.


Pharmacotherapeutic group: immunomodulator, ATC: L03AX.

Registered for melanoma treatment and as an immunomodulator.

Dosage: As recommended by physician along with concurrent tests.
...Today we can be proud that Rigvir is not only our success story, but at the same time it is a real help and hope for cancer patients not only in Latvia, but all around the world...”

“...In the sixties of the last century Latvian scientists proved the ability of viruses to fight malignant tumours by adapting a specific virus that was named Rigvir (Riga virus). In the next decades, scientists worked actively to prove effectiveness of the virus in various preclinical and clinical trials both in Latvia and in the rest of the world. In 2004 Rigvir was registered as a cancer-treating medicine and in 2005 the Latvian Academy of Sciences acknowledged Rigvir as one of the greatest inventions in Latvia...”

- Ingrida Circene. M.D.
Minister of Health, Republic of Latvia

“...To treat cancer with a virus is a fantastic idea which occurred in the beginning of the last century. Before the World War I, cancer was already treated with the rabies virus vaccine and other viruses. I managed to find a virus which is not dangerous for a man. This virus can be found in intestines of healthy children. Unlike the chemo and the radio therapies, this medicine does not leave such serious consequences in patient’s organs. The world began to speak in the beginning of the ’90s about what I have discovered in the ’70s. While reading conclusions drawn by Japanese and American scientists, I had a feeling that I am going through my own book...”

- Aina Muceniece, M.D., Dr. Med. Habil.
Inventor of Rigvir, Honorable Member of Latvian Academy of Sciences (1992), Emeritus Scientist (Immunology, Oncology, and Virology), Cross of Recognition for Special Services for the Benefit of

Cancer virotherapy is one of the most promising modern cancer therapy methods. Therefore, the leading countries in the development of pharmaceutical products have largely involved in virological researches with the aim of finding the most effective and safest viruses with the ability to selectively destroy malignant cells. Nobody doubts any more that viruses are able to do it. Just like nobody doubts any more that Latvia through Rigvir has become the leader and, at the same time, the pioneer in virotherapy. Virotherapy can be more effective, safer, and patient-caring than the cancer treatment methods known until now.”

- Professor Ivars Kalvins, Dr. Habil. Chem.
Director, Latvian Institute of Organic Synthesis; Member, European Academy of Sciences and Arts, and Latvian Academy of Sciences; Certificate & Gold Medal of World Intellectual Property Organization (WIPO) for long term and highly productive work as an inventor.
WOULD YOU LIKE TO FIND OUT IF RIGVIR® IS THE RIGHT TREATMENT FOR YOU?

Contact us for a free evaluation to find out if Rigvir® is the right treatment for your condition. Get your questions answered!

info@hope4cancer.com

1-888-544-5993 (Toll Free USA)
+1-619-669-6511 (International Callers, Outside USA)

ARE YOU A HEALTH PROVIDER LOOKING TO LEARN MORE ABOUT HOW YOU CAN INCLUDE RIGVIR® IN YOUR RECOMMENDATIONS?

Hope4Cancer® Institute partners with doctors in different capacities to offer integrative cancer treatments to patients worldwide. If you are interested in treatment with Rigvir®, please email us at doctor@hope4cancer.com.
Hope4Cancer® Institute has received accreditation from the Latvian Virotherapy Center as an approved institution meeting all the requirements for treatment of cancer patients with Rigvir®. Hope4Cancer® works closely with the Latvian Virotherapy Center (www.virotherapy.eu).