Zacks Small-Cap Research

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Novelos Therapeutics, Inc. (NVLT-OTCQX)

NVLT: Unique platform technology targets cancer imaging and therapy market – initiating with Outperform.

Current Recommendation	**Outperform**
Prior Recommendation	N/A
Date of Last Change	04/13/2012
Current Price (04/12/12)	$0.95
Twelve- Month Target Price	**$2.50**

OUTLOOK

Novelos' platform technology includes three candidates with chemically identical core structure. The three candidates target cancer imaging (LIGHT), cancer radiotherapy (HOT) and cancer chemotherapy (COLD) markets respectively.

All three candidates specifically target cancer and cancer stem cells, which offers advantages over other cancer compounds such as selectivity and broad spectrum of cancer types.

Development risk for HOT is lower than other early stage candidates due to its unique chemical structure and mechanism of action. Current valuation is low and we initiate coverage with an Outperform.

SUMMARY DATA

52-Week High	**$3.00**
52-Week Low	**$0.37**
One-Year Return (%)	**-32.14**
Beta	**0.75**
Average Daily Volume (sh)	**51,494**
Shares Outstanding (mil)	**37**
Market Capitalization ($mil)	**$35**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**61.2**
Insider Ownership (%)	**35.6**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2012 Estimate	**N/A**
P/E using 2013 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**High,**
Type of Stock	**Small-Blend**
Industry	**Med-Biomed/Gene**
Zacks Rank in Industry	**N/A**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2011	0.00 A	0.00 A	0.00 A	0.00 A	0.00 A
2012	0.00 E	0.00 E	0.00 E	0.00 E	0.00 E
2013					0.00 E
2014					0.25 E

Earnings per Share
(EPS is operating earnings before non recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2011	-$0.06 A	-$0.10 A	-$0.07 A	-$0.07 A	-$0.31 A
2012	-$0.06 E	-$0.06 E	-$0.05 E	-$0.06 E	-$0.23 E
2013					-$0.19 E
2014					-$0.15 E

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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KEY POINTS

- We are initiating coverage of Novelos (NVLT) with an Outperform rating. Our 12-month price target is $2.50.

- Novelos is a development stage pharmaceutical company. The Company's unique technology specifically targets cancer and cancer stem cells through interaction with lipid rafts which are enriched in cancer and cancer stem cells.

- The advantages the Company's technology lie in its selectivity of cancer-targeting as well as broad spectrum of anticancer activity. Since the lipid rafts are enriched in cancer and cancer stem cells, the Company's three candidates all selectively target these cancer and cancer stem cells. Because lipid rafts are overexpressed in most of cancer and cancer stem cells, this makes the Company's candidates target many types of cancers.

- LIGHT has the potential to become the new standard of care for cancer PET imaging due to its selectivity for cancer/cancer stem cells over FDG, current standard of care for cancer PET imaging. LIGHT also has the advantage of delivery range due to its four-day half-life versus F-18 labeled FDG's 110 minutes half-life.

- The specific targeting of both cancer and cancer stem cells makes NVLT's HOT/COLD with the efficacy potential to target all three major drivers of mortality in cancer –**primary tumors**, **metastases** and stem cell-based **relapse**, which distinguishes HOT/COLD from all other cancer therapy modalities.

- As a new systemic radiotherapy, HOT has the advantage over existing systemic radiotherapeutic Zevalin and Bexxar. The selective interaction with lipid rafts makes HOT a **broad spectrum** cancer targeting agent since lipid rafts are overexpressed in most of cancer and cancer stem cells. Selective uptake and retention of HOT in cancer stem cells compared with normal cells also offer the prospect of **longer lasting cancer remission**.

- We believe **development risk is relatively less for HOT** than other early stage cancer therapeutics. HOT exploits a new cancer-selective delivery and retention mechanism, but is paired with a proven and effective radioisotope (I-131) for therapy. Because the therapeutic properties of the iodine-131 are well known, the risk of non-efficacy in human clinical trials is less than that of other cancer therapies at this stage of development. Furthermore, LIGHT PET imaging data is expected to predict efficacy and enable calculation of efficacious doses of HOT for Phase II trials (i.e. LIGHT serves as an ideal and personalized biomarker for HOT).

- This is important for investors because less development risk means that HOT has a higher probability for success in clinical trials and regulatory approval. Therefore, downside risk is reduced while upside potential remains the same.

- Current valuation is low in our view. The risk/return profile is biased to return at this point.

OVERVIEW

Novelos Therapeutics, Inc. (NVLT) is a development stage pharmaceutical company focused on the development of compounds for the **diagnosis and treatment of cancer**.

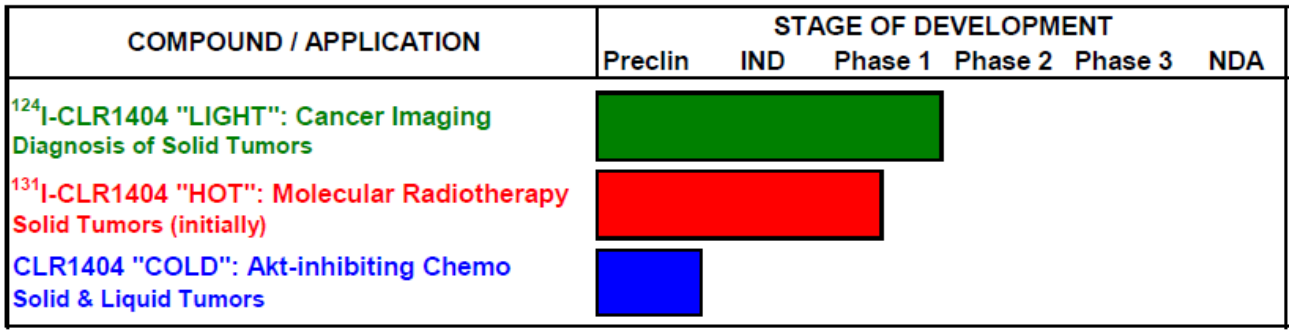
On April 8, 2011, Novelos entered into a business combination with **Cellectar, Inc**. a privately held Wisconsin corporation that designs and develops products to detect, treat and monitor a wide variety of human cancers. The acquisition added three new compounds into Novelos' pipeline.

These three new drug candidates are nicknamed as LIGHT, HOT and COLD, which are cancer-targeted compounds. All three compounds are selectively taken up and retained in cancer cells, including cancer stem cells, versus normal cells. This offers the potential for a paradigm shift in cancer therapy by providing efficacy versus all three major drivers of mortality in cancer: **primary tumors**, **metastases** and **stem cell-based relapse**.

Novelos, through the acquisition of Cellectar, obtained exclusive rights to the related technology patents from University of Michigan in 2003 and continued development of the platform while obtaining ownership of numerous additional patents and patent applications (lasting until 2025, 2028 and 2030 without extensions) prior to the acquisition.

I-124-CLR1404 (LIGHT) is a small-molecule cancer-targeted positron emissions tomography (PET) imaging agent. LIGHT has first-in-class potential and **Phase I/II** clinical trials are ongoing. **I-131-CLR1404 (HOT)** is a small-molecule, broad-spectrum, cancer-targeted molecular radiotherapeutic that delivers cytotoxic (cell-killing) radiation directly and selectively to cancer cells and cancer stem cells. HOT also has first-in-class potential. HOT **Phase Ib** dose-escalation trial is ongoing and could enter into Phase II trials in the first quarter of 2013 as a monotherapy for solid tumors with significant unmet medical need, subject to additional funding. **CLR1404 (COLD)**, a cancer-targeted non-radioactive chemotherapy, works primarily through Akt (a serine/threonine protein kinase) inhibition. In preclinical studies, COLD continues to show promise in cancer and cancer stem cell therapy. NVLT is currently focused on clinical stage compounds, LIGHT and HOT.

Together, these three compounds are able to "find, treat and follow" cancer anywhere in the body in a novel, effective and highly selective way.



Novelos is headquartered in Madison, Wisconsin.

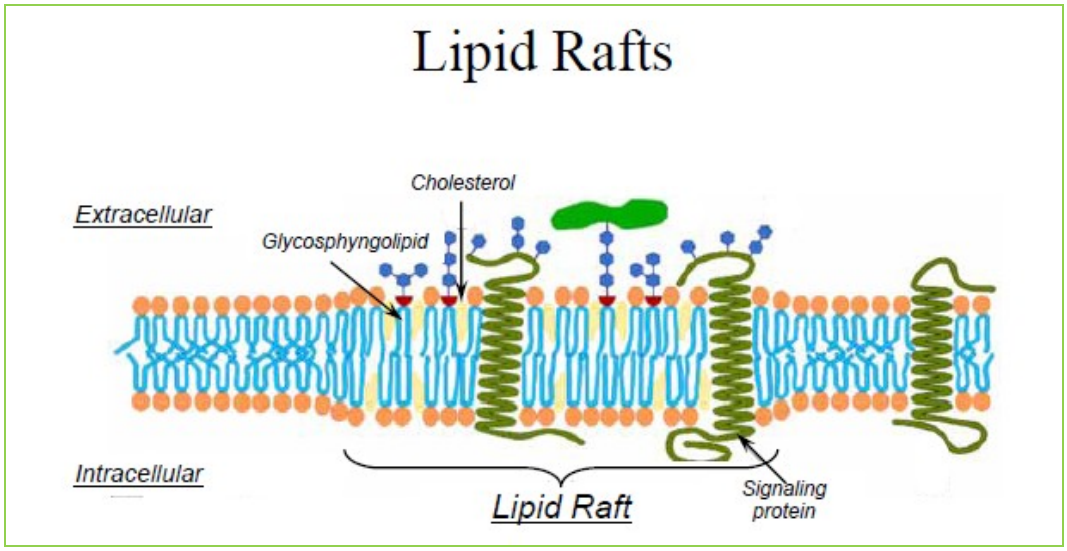
INVESTMENT THESIS

Technology Overview

The acquisition of Cellectar has transformed Novelos with new technology and new candidates. The Company's compounds are called **phospholipid ethers (PLEs)** that interact with lipid rafts.

Lipid rafts are low-density, detergent-resistant microdomains of plasma membrane that are enriched in cholesterol and glycosphingolipids. Lipid Rafts are known to be abundant in various signaling molecules, such as cell surface receptors and intracellular signaling molecules, and thus, these microdomains have

been involved in many cellular functions, including the regulation of apoptosis and cell proliferation. Studies have shown that cancer and cancer stem cells are enriched in lipid rafts. Therefore, **Lipid rafts are promising targets in cancer therapy and diagnosis.**



Source: Company presentation

The basis for selective tumor targeting of PLEs lies in differences between the plasma membranes of cancer cells as compared to those of most normal cells. Specifically, cancer and cancer stem cell membranes are highly enriched in lipid rafts. Disruption of lipid raft architecture suppresses uptake of radiolabeled COLD into cancer cells.

Lipid rafts are central to the activity of Novelos compounds in two ways:

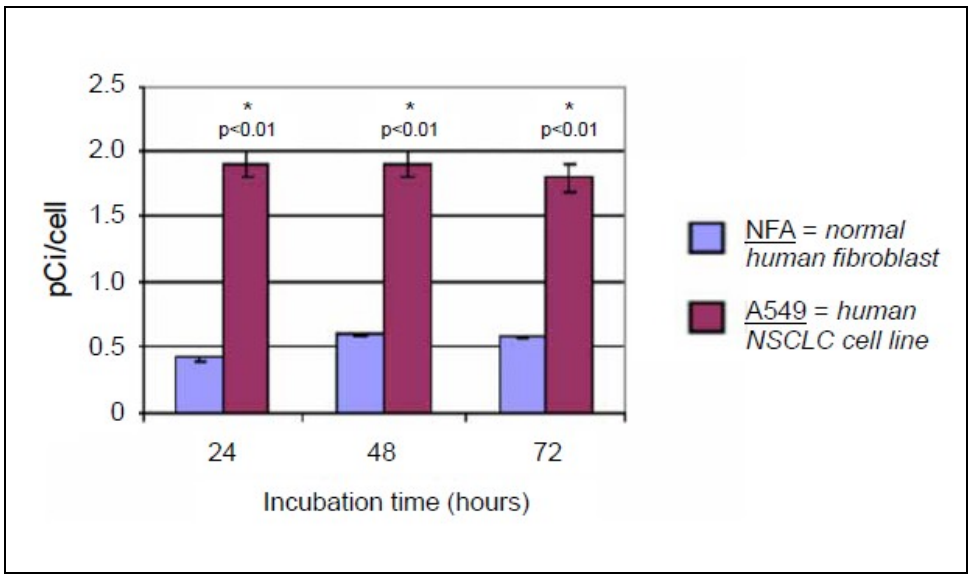
- Lipid rafts are portals of entry for PLEs such as LIGHT, HOT and COLD. The marked selectivity of PLEs for cancer cells versus non-cancer cells is due to the fact that cancer cells have far more lipid rafts. In addition to accumulating in lipid rafts, LIGHT, HOT and COLD are transported into the cytoplasm, where they distribute to organelle membranes (mitochondria, ER, lysosomes) but not the nucleus.

- Lipid rafts also regulate signaling-based cell functions including apoptosis and cell proliferation, and PLEs disrupt this regulation. One key signaling pathway that is regulated by interactions with lipid rafts is the phosphatidylinosotol 3-kinase (PI3K)/**Akt pathway**. Activation of Akt pathway is involved in cell growth and proliferation. COLD pharmacologically inhibits the activation of Akt. In cancer cells, Akt inhibition is associated with induction of apoptosis and decreased cell proliferation/survival.

NVLT's three drug candidates share the core chemical structure, which are designed to provides **selective targeting** of cancer cells, including cancer stem cells, in preference to normal cells through selective interaction with lipid rafts (due to enrichment of lipid rafts in cancer and cancer stem cells). The following chart demonstrates the selective targeting of cancer cells by **^{125}I-labeled COLD**.

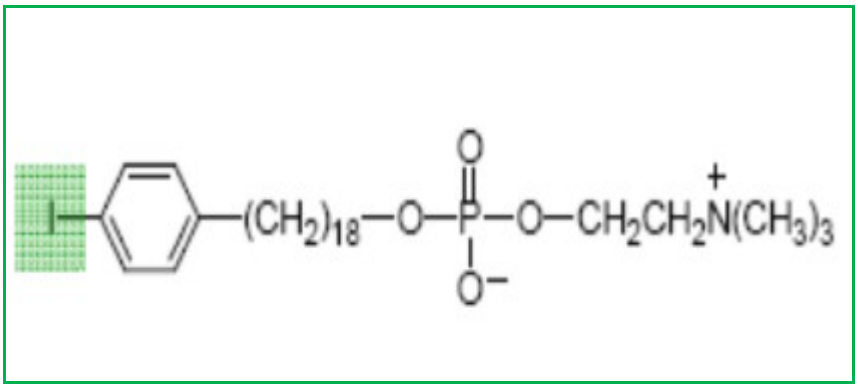
- ^{125}I-labeled COLD was present in the media throughout the experiment.
- Cells were incubated with 2µCi of ^{125}I –COLD for the time points indicated and the media was removed.
- The cells were washed with 1XPBS+0.1%BSA, trypsinized, and split into two samples for determination of cell number by DNA content and counts per minute.
- Data is displayed as (radio) Activity per cell (pCi/cell).

- The results: Normal cells took up little ^{125}I –COLD, while NSCLC cells had a higher level of ^{125}I –COLD, indicating the selective targeting of cancer cells by ^{125}I –COLD.



Source: Company presentation

COLD was deliberately designed to contain iodine (in the form of the stable, non-radioactive isotope, I-127), thus enabling additional, distinct products differing only with respect to the form of iodine they contain. **HOT** contains short-lived radioactive I-131 and **LIGHT** contains the even more short-lived radioactive I-124.



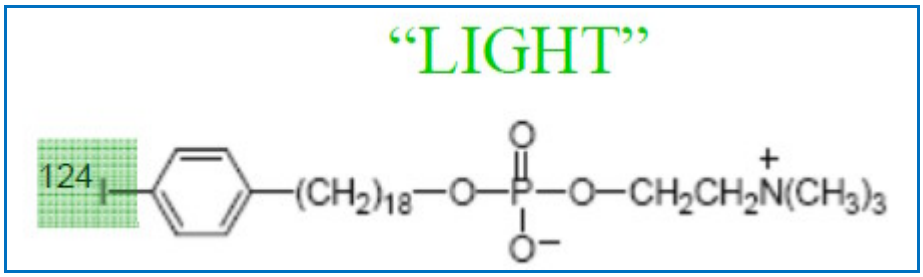
As a result, three cancer-targeted product profiles have been generated from a single chemical structure that is the foundation of the technology platform – a **chemotherapeutic** agent, COLD, a molecular **radiotherapeutic** agent, HOT and a **diagnostic/imaging** agent, LIGHT.

The specific targeting of both cancer and cancer stem cells makes NVLT's HOT/COLD with the efficacy potential to target all three major drivers of mortality in cancer –**primary tumors**, **metastases** and stem cell-based **relapse**, which distinguishes HOT/COLD from all other cancer therapy modalities.

	Primary Tumors	Metastases	Relapse
HOT / COLD	**Treats**	**Treats**	**Prevents**
Non-specific Chemotherapy	Treats	Treats	n/a
Molecular Targeted Chemotherapy	Treats	Treats	n/a
Surgery	Treats	Does not treat	n/a
External Radiation	Treats	Does not treat	n/a

LIGHT (I-124-CLR1404) for Cancer Imaging

LIGHT is a small-molecule **imaging agent** that has first-in-class potential for selective detection of tumors and metastases in a broad range of cancers. LIGHT is comprised of a small, non-pharmacological quantity of CLR1404 (COLD, acting as a cancer-targeted delivery and retention vehicle) labeled with the shorter-lived radioisotope, iodine-124, a new PET imaging isotope. Chemically, LIGHT is 18-(p-[I-124]iodophenyl) octadecyl phosphocholine, identical to COLD except that the iodine is the radioactive isotope, I-124, which has a radiation half-life of 4 days.



PET imaging used in conjunction with CT scanning has now become the imaging method of choice in oncology. In studies to date, LIGHT selectively illuminated malignant tumors in 52 of 54 animal models of cancer, demonstrating evidence of broad-spectrum, cancer-selective uptake and retention.

An investigator-sponsored **Phase I/II** trial of LIGHT as a PET imaging agent for **lung cancer** was initiated in December 2011 at the University of Wisconsin Carbone Cancer Center (UWCCC) and first patient was enrolled in February 2012. Dr. Anne M. Traynor at UWCCC is conducting the Phase I/II trial. Novelos provides funding for the trial and the data is shared with Novelos while the study progresses and at the conclusion of the study. Up to 12 patients will be enrolled across two dose levels (3 mCi and 5 mCi) in this Phase I/II trial. Initial data are expected to be available in 2Q12. The trial will be completed in 2012.

Another investigator-sponsored **Phase I/II** trial of LIGHT as a PET imaging agent for **brain cancer** was initiated in December 2011 at UWCCC and first patient was enrolled on March 15, 2012. Dr. Lance Hall at the UWCCC is conducting the Phase I/II trial. This trial is being funded by an Institute for Clinical and Translational Research (ICTR) grant, whereas the data is shared with Novelos while the study progresses and at the conclusion of the study. Up to 20 patients will be enrolled at a 5 mCi dose. Initial data are expected to be available in 2Q12. The trial will be completed in early 2013.

An investigator-sponsored **Phase I/II** trial of LIGHT as a PET imaging agent for **metastatic brain cancer** was initiated in January 2012 at UWCCC and first patient is expected to be enrolled in 2Q12. This trial is being funded by a $1.2 million grant from the National Cancer Institute.

Starting in the second quarter of 2012, Novelos also expects to initiate LIGHT imaging trials in various other solid tumors.

These Phase I/II trials, if successful, will serve two important purposes :

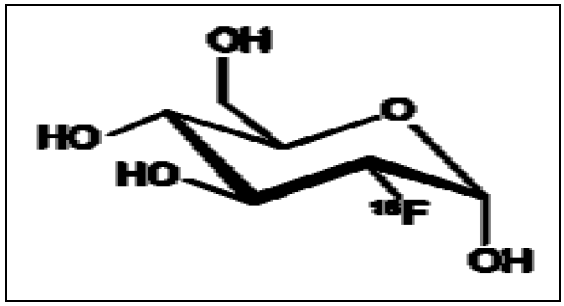
- Establish LIGHT as cancer-selective PET imaging agent
  - pre-therapy ("FIND"): diagnosis, staging, tumor baseline
  - post-therapy ("FOLLOW"): evaluate therapeutic efficacy
- Accelerate development of **HOT**
  - as predictor of efficacy
  - calculate effective dose for Phase II trials

LIGHT has the potential to supplant the current "gold standard" agent, 18-fluoro-deoxyglucose (**FDG**), due to its superior cancer-specificity and more favorable logistics of clinical use.

We believe positive data would establish proof-of-concept for LIGHT as a PET imaging agent for this indication, and could advance partnering discussions.

Market Potential for LIGHT

Currently, 18-fluoro-deoxyglucose (FDG) is the **standard of care** for cancer PET/CT imaging. ^{18}F-FDG is taken up by cells, and retained by tissues with high metabolic activity, such as most types of malignant tumors. As a result FDG-PET can be used for diagnosis, staging, and monitoring treatment of cancers, where a static ^{18}F-FDG PET scan is performed and the tumor ^{18}F-FDG uptake is analyzed in terms of standardized uptake value (SUV).



Sales of ^{18}F-FDG were approximately $400 million in 2007. Sales in 2011 were estimated to be over $500 million and are estimated to grow to exceed over $1 billion by 2014. This is a big market for LIGHT when it reaches the market.

LIGHT Offers Significant Advantages Versus FDG

FDG accumulates in any tissue having increased glucose metabolism compared to surrounding tissue. As a result and in contrast to LIGHT, **FDG is not selective** for malignant tumors. FDG localizes in certain normal tissue such as heart and brain tissues that also have high glucose metabolism. FDG is also known to localize in inflammatory sites. Other major limitations to the use of FDG are found in pelvic imaging due to the high renal (kidney) clearance of the compound. These characteristics of FDG, therefore, decrease its diagnostic specificity for certain malignancies. FDG is no longer covered by patent and is typically manufactured onsite at PET imaging medical facilities because of its limited (110 minute) half-life.

The Company compared LIGHT and FDG side by side (24 hours apart) in the same tumor-bearing mouse that was also treated with carageenan to induce inflammation. As expected, FDG demonstrated significant uptake into the inflammatory lesion and organs such as heart and bladder compared to the malignant tumors, which were poorly imaged. LIGHT, on the other hand, showed no uptake into the inflammatory lesion and organs, yet clear and demonstrable uptake into the tumors.

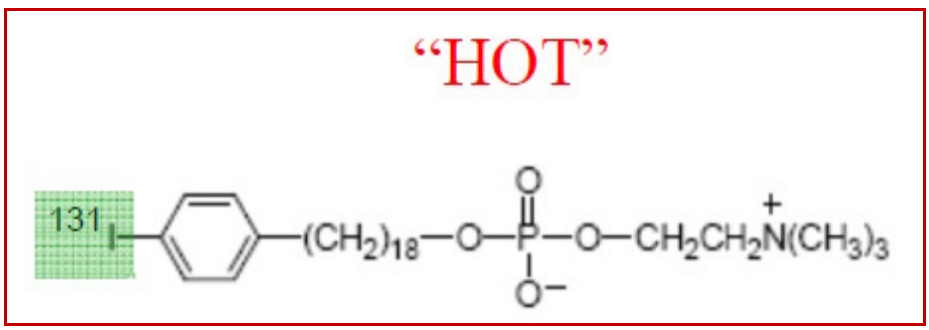
Additionally, the radioisotopic half-life of only 110 minutes for fluorine-18 labeled agents, such as FDG, severely limits their **delivery range** relative to the point of manufacture. I-124 has a four-day half-life that permits worldwide distribution of LIGHT from one manufacturing location. Additionally, the longer half-life affords a longer imaging window of up to seven days following injection.

With advantages over FDG, we think LIGHT has the potential to become new standard of care for cancer PET imaging. Peak sales could reach $500 million in 5 years. The following table summarizes LIGHT advantages versus FDG:

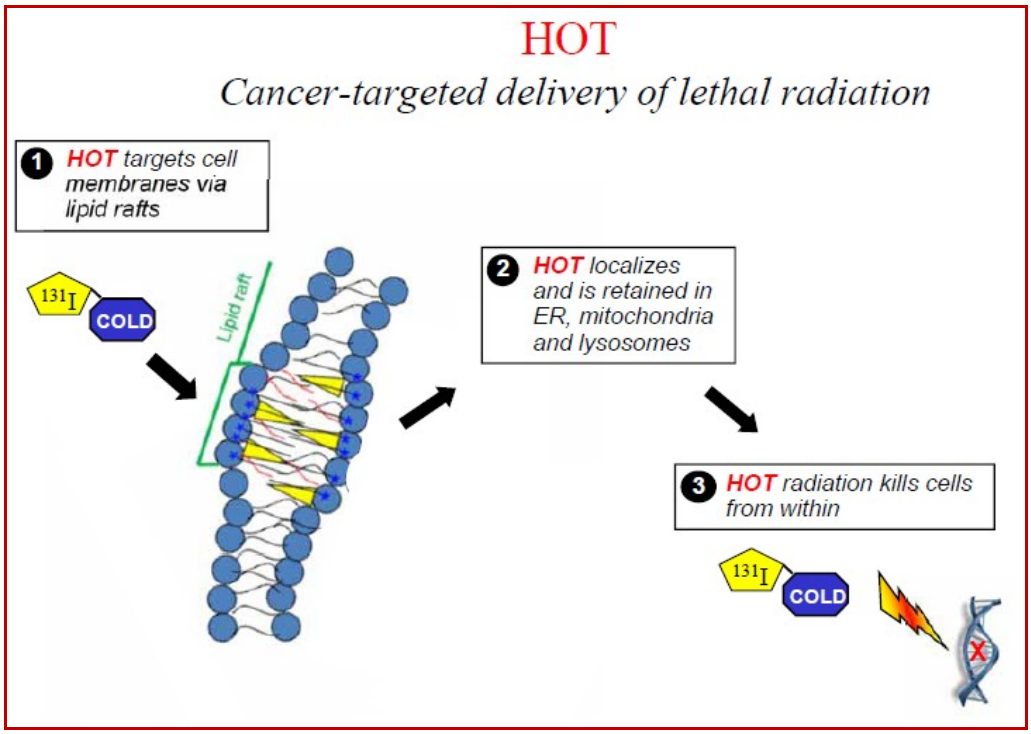
	LIGHT	FDG
Specificity	Cancer-specific	Not cancer-specific *(labels any high metabolic rate tissue)*
Spectrum	+++	++
Logistics of use	Can be used distant from production site (4 day t½)	Must be used close to site of production (110 min t½)
Cost	Similar	

HOT (I-131-CLR1404) for Cancer Radiotherapy

Chemically, HOT is 18-(p-[I-131]iodophenyl) octadecyl phosphocholine, identical to COLD except that the iodine in its structure is the radioactive (“hot”) isotope, I-131, which has a radiation half-life of eight days.



HOT is a small-molecule, broad-spectrum, cancer-targeted molecular radiotherapeutic that has first-in-class potential. HOT is comprised of a small, **non-pharmacological quantity** of CLR1404 (COLD), acting as a cancer-targeted delivery and retention vehicle and incorporating a cytotoxic dose of **radiotherapy** (in the form of iodine-131, a radioisotope that is already in common use to treat thyroid and other cancer types).



Source: Company presentation

Preclinical in vitro (in cell culture) and in vivo (in animals) experiments have demonstrated selective killing of cancer cells along with a benign safety profile of HOT. Significant anti-tumor/survival-prolonging activities have been demonstrated in more than a dozen xenograft models (human tumor cells implanted into animals) including breast, prostate, lung, glioma (brain), pancreatic, ovarian, uterine, renal and colorectal cancers and melanoma. In all but two models, a single administration of a well-tolerated dose of HOT was sufficient to demonstrate efficacy.

HOT was also tested in combination with a standard efficacious dose of **gemcitabine** in a pancreatic cancer xenograft model. Single doses of HOT or gemcitabine given alone were equally efficacious while the combination therapy was significantly more efficacious than either treatment alone (additive). In each xenograft study, the dose of HOT was ~100 µCi, which is at least 50% less than the maximum tolerated dose in mice.

In early 2010, Novelos completed a **Phase Ia** dosimetry trial, which demonstrated initial safety, tumor imaging and pharmokinetic consistency. Single IV doses of 10 mCi **HOT** was administered in 8 patients with relapsed or refractory advanced solid tumors. HOT was well tolerated, no severe adverse events (SAEs) were observed. All AEs were considered minimal, manageable and not dose limiting. Limited tumor imaging plus analysis of total body imaging and urine samples collected over 42 days indicated that **HOT** reached target cancer lesions and that exposure was sustained. The trial established an initial dose of 12.5 mCi / m2 for the Phase Ib escalating dose trial.

Based on the Phase Ia data, Novelos initiated a **Phase 1b** dose-escalation / MTD trial in November 2011. First patient was enrolled in Jan 2012. For each subject, the study will be conducted in two phases, dosimetric and therapy. In the **dosimetric phase**, subjects will receive one 5 mCi dose of the study drug

and undergo whole body imaging on the day of infusion and on post-infusion days 1, 2, 3, and 6 for assessment of biodistribution of I-131-CLR1404. If normal and expected biodistribution are demonstrated, the subject will begin the therapy phase. In the **therapy phase**, the first cohort of subjects will receive a dose of 12.5 mCi/m2. Dose escalation in subsequent cohorts will initially be in increments of 12.5 mCi/m2. Subjects will be followed and observed for unacceptable toxicity through 56 days after the therapy dose infusion with follow-up for up to one year.

The primary objective of this Phase Ib dose-escalation trial in patients with a range of advanced solid tumors is to define the Maximum Tolerated Dose (MTD) of HOT. In addition to determining the MTD, the Phase Ib trial is intended to evaluate overall tumor response (using standard RESIST I criteria) and safety.

The Company plans to initiate **Phase IIa** studies as a **monotherapy** for solid tumors in 1Q2013 as soon as a minimal efficacious dose is established, if additional funding can be secured. Novelos will determine the minimal efficacious dose upon seeing a tumor response in the Phase Ib trial or calculating it from ongoing PET imaging trials in cancer patients with LIGHT (since PET imaging is quantitative, enabling determination of tumor radiation exposure at a given dose level). The target cancer will be NSCLC, triple-negative breast cancer, brain cancer, soft tissue sarcoma, etc.

Since HOT has demonstrated synergistic efficacy when used in combination with chemotherapeutics in animal models, the Company plans to explore **HOT combination with chemotherapeutic agents** for the treatment of cancers if funds are available. A number of chemotherapeutic agents are known to be radiosensitizers and could have the potential to enhance the efficacy of HOT. Combination therapy could greatly expand HOT usage in a variety of cancers and could enhance its commercial potential as a cancer therapeutic.

Advantages of HOT Over Existing Systemic Radiotherapies

Radiation therapy, along with surgery and chemotherapy, is one of the three major modalities for cancer treatment. The goals of targeted cancer radiotherapy — selective delivery of effective doses of isotopes that destroy tumor tissue, sparing of surrounding normal tissue, and non-accumulation in vital organs such as the liver and kidneys — remain goals of novel therapies as well.

In systemic radiation therapy, a patient swallows or receives an injection of a radioactive substance, such as radioactive iodine or a radioactive substance bound to a monoclonal antibody. Currently, the two commonly used systemic targeted radiotherapies are **Zevalin®** (90Y, Spectrum Pharmaceuticals) and **Bexxar®** (I-131, GSK).

Zevalin® (ibritumomab tiuxetan) has been approved by the FDA for the treatment of certain types of B-cell non-Hodgkin lymphoma (NHL). The antibody part of this drug recognizes and binds to a protein called CD-20 found on the surface of B lymphocytes. The combination drug regimen of tositumomab and iodine I-131 tositumomab (Bexxar®) has also been approved for the treatment of certain types of NHL. In this regimen, tositumomab recognizes and binds to the same protein on B lymphocytes as ibritumomab. The nonradioactive form of the antibody helps protect normal B lymphocytes from being damaged by radiation from ^{131}I.

Both Zevalin and Bexxar have limitations as systemic cancer radiotherapy. In both cases, tumor-targeting is monoclonal antibody-based and limited to non-Hodgkins lymphoma. Although antibody has excellent selectivity, but it has limited therapeutic utility (only one type of tumor).

The beauty of HOT design is that HOT **selectively** targets cancer and cancer stem cells due to enrichment of lipid rafts in these cells. The interaction with lipid rafts also makes HOT a **broad spectrum** cancer targeting agent since lipid rafts are overexpressed in most of cancer and cancer stem cells.

Notably, both Zevalin® and Bexxar® were approved on the basis of objective response rates (shrinking of tumors) without data to support improvement in survival. Selective uptake and retention of HOT in cancer stem cells compared with normal cells also offer the prospect of **longer lasting cancer remission**.

Development Risk for HOT is Less Than Other Early Stage Cancer Therapeutics

The less development risk for HOT is determined by the chemical structure and the mechanism of action of HOT. HOT exploits a new cancer-selective delivery and retention mechanism, but is paired with a proven and effective radioisotope (I-131) for therapy.

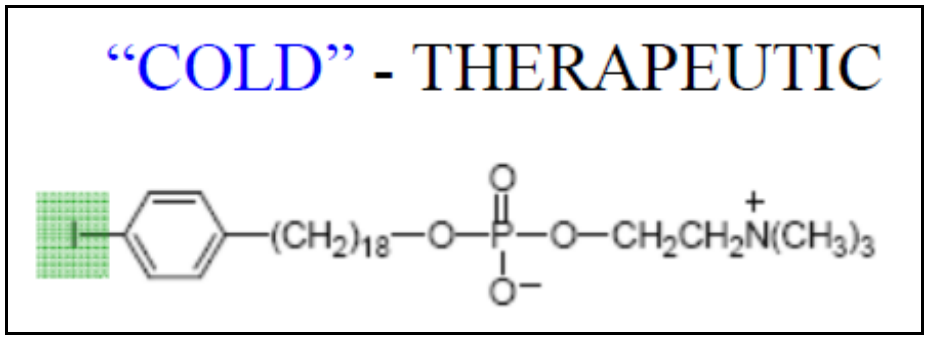
We believe that HOT is not subject to the full extent of development risk typically associated with other early-stage cancer therapeutics for the following reasons:

- HOT is selectively taken up by and retained in cancer versus normal cells and its delivery vehicle (COLD) is intended to be given to patients in sub-pharmacological doses, resulting in an improved safety profile compared to standard chemotherapy.
- HOT does not rely on inhibition or enhancement of a specific pathway; it works by exposing cancer cells to sustained lethal radiation from within.
- Because the therapeutic properties of the iodine-131 are well known, the **risk of non-efficacy in human clinical trials is less** than that of other cancer therapies at this stage of development.
- To date, HOT (as demonstrated with LIGHT studies) has shown near-universal cancer-specific retention in more than 50 *in vivo* tumor models, making the molecule potentially effective in numerous cancer types (**broad-spectrum**) as compared to type-specific therapies.
- HOT is a small molecule that is easily characterized and synthesized and is therefore not subject to scale-up and manufacturing risks typically associated with large molecules such as monoclonal antibodies.

The less development risk means that HOT has a higher probability for success in clinical trials and regulatory approval.

Cold, Potential to be Best in Class for Chemotherapy

Chemically, COLD is 18-(p-[I-127] iodophenyl) octadecyl phosphocholine. The iodine atom in its structure is the stable, non-radioactive (“cold”) isotope, I-127.



COLD is a cancer-targeted chemotherapy that inhibits the **Akt/protein kinase B (PKB) survival pathway** and induce apoptosis.

The Akt/PKB pathway, which is activated by growth factors such as PDGF (platelet-derived growth factor), EGF (epidermal growth factor), and insulin, is overactive in many human cancers and contributes

to cell growth, proliferation, survival and resistance to radiation and chemotherapeutics. Recent studies have suggested that lipid rafts are implicated in Akt activation, therefore involved in cancer cell proliferation.

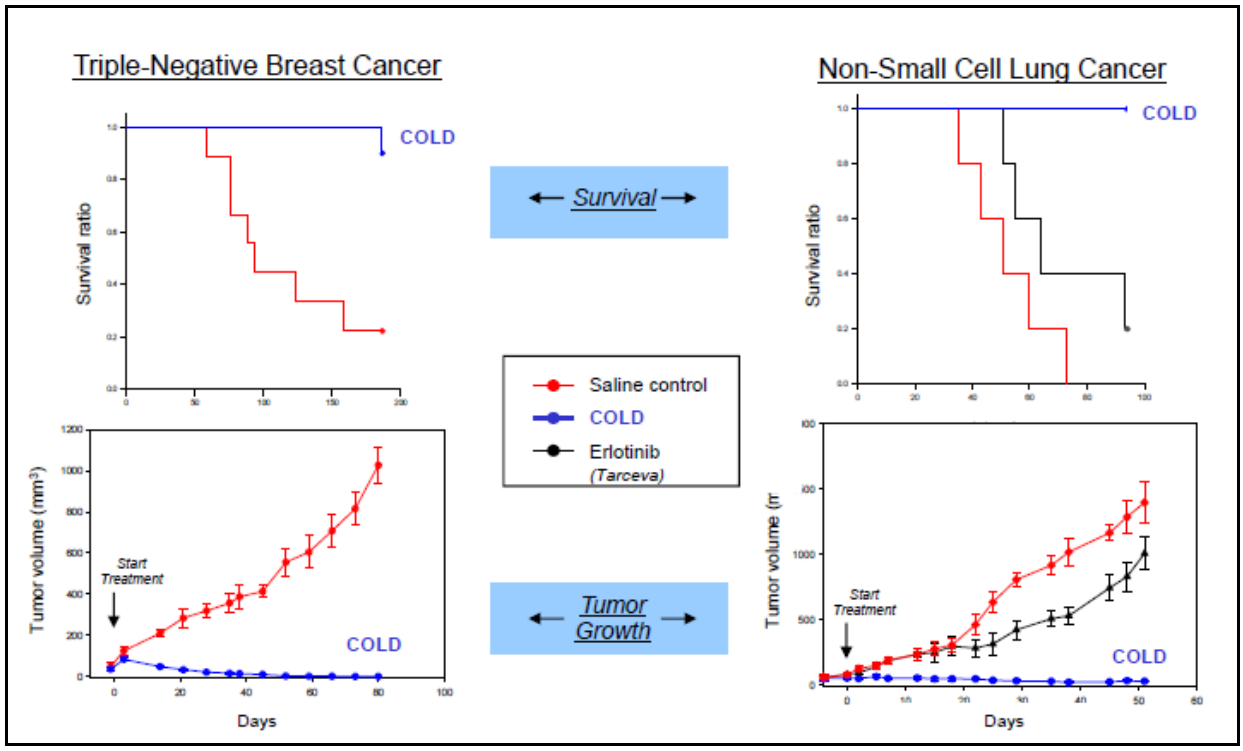
COLD selectively inhibits Akt activation in human cancer cells compared to normal proliferating cells. COLD induces apoptosis through **caspase** activation and suppresses proliferation in a wide range of human cancer cell lines including prostate carcinoma, ovarian carcinoma, triple-negative breast carcinomas, pancreatic adenocarcinoma and non-small cell lung cancer. At these concentrations, COLD does not inhibit proliferation of normal cells.

COLD has the potential to be best-in-class versus other Akt inhibitors in development and COLD has important advantages over competitor agents including:

- **Selective uptake and retention** by cancer cells/cancer stem cells compared to normal cells/stem cells. This results in significantly greater potency of COLD as an inhibitor of cell proliferation in cancer cells versus normal cells, and

- **Suitability for intravenous administration**, avoiding dose-limiting gastrointestinal toxicity seen with orally administered Akt-inhibiting **phospholipid ether (PLE)** and potentially enabling greater systemic drug exposure and, hence, Akt-inhibition in cancer cells, resulting in superior efficacy.

COLD has shown selective inhibition of Akt activity in many cancer cell lines. COLD has also demonstrated significant in vivo efficacy in mouse xenograft tumor models, including non-small cell lung cancer and triple-negative breast cancers, producing long-lasting tumor growth suppression and significantly increased survival.



Source: company presentation

The development path for COLD includes evaluation in a standard battery of IND-enabling pre-clinical tests and scaled-up manufacture. In parallel, Novelos intends to test COLD in mouse xenograft tumor models in combination with standard chemotherapeutic agents to demonstrate synergies. These

additional pre-clinical data will enable estimation of COLD plasma levels associated with in vivo efficacy, establish a starting dose for the initial Phase I clinical trial and facilitate selection of target indications.

The Company initially planned to submit an IND application to the FDA in the first quarter of 2013, but has put COLD further development on hold until they find out what went wrong with perifosine, which recently failed pivotal Phase III trials. Currently, Novelos is focused on its clinical stage compounds, LIGHT and HOT.

An Experienced Management Team

Harry S. Palmin, President and CEO

Mr. Palmin has served as president and a director since 1998 and chief executive officer since January 2005. From 1998 to September 2005, he served as acting chief financial officer. From 1996 to 1998, he was a vice president at Lehman Brothers and from 1993 to 1996, he was an associate at Morgan Stanley & Co.

Mr. Palmin earned a B.A. in economics and business and a M.A. in international economics and finance from the International Business School at Brandeis University. He has also studied at the London School of Economics and the Copenhagen Business School. Mr. Palmin's experience managing the funding and development of the Company's product candidates for 13 years and his knowledge of capital markets are strong qualifications to serve on the Company's board of directors.

J. Patrick Genn, VP, Investor Relations

Mr. Genn was appointed vice president of investor relations in December 2011. He has 28 years of senior management experience in finance, banking and investment management. Mr. Genn was previously President of Continuum Investment Holdings, Inc. from 2006 through mid-2010 while serving on the board of directors of several biotech and technology companies including Cellectar, Inc. From 2001 through 2005, he was an advisor and consultant to several companies including Carmel Valley Ventures and Continuum Investment Partners. Mr. Genn held several senior management positions at Wells Fargo between 1987 and 2001. He was a member of the senior management team that launched the mortgage lending division in 1987 and the premier banking division in 1993. He was also a member of the core mergers and acquisitions integration team and managed private client services in San Diego, CA.

Mr. Genn received a B.B.A. in Marketing and a M.S. in Product Management from the University of Wisconsin-Madison.

Kimberly A. Hawkins, VP, Clinical Development

Ms. Hawkins has served as vice president of clinical development since November 2010 and served as director of clinical development since May 2006. She has worked for 17 years in the biopharmaceutical industry managing and overseeing clinical operations for multiple global Phase 1, 2 and 3 clinical studies. From 2001 to 2006, Ms. Hawkins was a senior manager in clinical development at Antigenics, Inc., a cancer biotechnology company where she managed multiple Phase 1 and 2 studies. From 1994 to 2001 she was employed by Genzyme Corporation, Center for Clinical Research Practice where she held the positions of clinical research associate, trainer of good clinical practice and study coordinator. From 1993 to 1994 she held the position of clinical research coordinator at Boston Medical Center.

Ms. Hawkins has a B.S. degree in Human Physiology from Boston University and a Master's Degree in Public Health from Boston University School of Public Health.

Christopher J. Pazoles, VP, R&D

Dr. Pazoles has served as vice president of research and development since July 2005. He has 30 years of biopharmaceutical research and development and senior management experience. From May 2004 to June 2005, he held a senior research and development position at the Abbott Bioresearch Center, a division of Abbott Laboratories. From October 2002 to January 2004, he served as chief operating officer and head of research and development at ALS Therapy Development Foundation. From 1994 to October 2002, Dr. Pazoles served as vice president of research for Phytera, Inc. From 1981 to 1994, he served as a researcher and senior manager with Pfizer.

Dr. Pazoles holds a Ph.D. in microbiology from the University of Notre Dame.

Joanne M. Protano, VP, CFO

Ms. Protano was appointed vice president, chief financial and accounting officer, and treasurer in December 2007. She has 20 years of finance and senior management experience. She previously held the position of Senior Director of Finance and Controller of the Company from June 2006 to December 2007. From 1996 to 2006, she held various management and senior management positions with Ascential Software, Inc. and predecessor companies including Assistant Controller, Reporting for Ascential Software, Vice President and Chief Financial Officer for the Ascential Software Division of Informix Software, Inc. and Corporate Controller of Ardent Software, Inc. Prior to her tenure in the technology industry, from 1990 to 1996 she was employed by Deloitte and Touche LLP as an audit manager, serving technology and healthcare clients.

Ms. Protano received a B.S. in business administration from Bryant College.

Jamey P. Weichert, CSO

Dr. Weichert was the primary founder of Cellectar serving as Cellectar's Chairman and Chief Scientific Officer since 2002. He was appointed as the Chief Scientific Officer and a director of Novelos at the time of the Acquisition. Dr. Weichert is an Associate Professor of the Departments of Radiology, Medical Physics, Pharmaceutics and member of the Comprehensive Cancer Center at the University of Wisconsin, Madison.

He has a bachelor's degree in chemistry from the University of Minnesota and a doctorate in medicinal chemistry from U. Mich. His research interests include the design, synthesis and evaluation of biomimetic CT and MRI imaging agents and diapeutic radiopharmaceuticals. He has been involved in molecularly targeted imaging agent development his entire professional career and has developed or co-developed several imaging agents nearing clinical trial status. Dr. Weichert serves or has served on the editorial boards of numerous scientific journals and has authored more than 40 peer reviewed publications and 150 abstracts. He also has 20 issued or pending patents related to drug delivery, imaging and contrast agent development. Dr. Weichert's experience founding and managing the development of Cellectar's product candidates and his knowledge of radiation technology are strong qualifications to serve on board of directors.

VALUATION AND RECOMMENDATION

We are initiating coverage of Novelos Therapeutics (NVLT) with an Outperform rating. Our 12-month target price is $2.50 per share.

NVLT's platform technology is unique. All three candidates are generated from a single chemical structure that is the foundation of the technology platform. The three candidates target three sub-cancer markets: cancer imaging (LIGHT), cancer radiotherapy (HOT) and cancer chemotherapy (COLD).

The beauty of the Company's technology is that all three candidates specifically target cancer and cancer stem cells through interaction with **lipid rafts** which are enriched in cancer or cancer stem cells. The specific targeting of both cancer and cancer stem cells makes NVLT's HOT/COLD with the efficacy potential to target all three major drivers of mortality in cancer –**primary tumors**, **metastases** and stem cell-based **relapse**, which distinguishes HOT/COLD from all other cancer therapy modalities.
All three candidates have demonstrated excellent safety profile and efficacy in preclinical trials including animal models. The Company has moved LIGHT and HOT into the clinic with both in Phase I/II clinical trials. Preliminary data from the clinical trials have also shown excellent safety profile and efficacy activity for both LIGHT and HOT, which is in line with preclinical results.

Both LIGHT and HOT have competitive advantages over their respective competitors. LIGHT has the potential to become the new standard of care for cancer PET imaging due to its selectivity for cancer/cancer stem cells over FDG, current standard of care for cancer PET imaging. LIGHT also has the advantage of delivery range due to its four-day half-life versus F-18 labeled FDG's 110 minutes half-life.

As a new systemic radiotherapy, HOT has the advantage over existing systemic radiotherapeutic Zavalin and Bexxar. The selective interaction with lipid rafts makes HOT a **broad spectrum** cancer targeting agent since lipid rafts are overexpressed in most of cancer and cancer stem cells. Selective uptake and retention of HOT in cancer stem cells compared with normal cells also offer the prospect of **longer lasting cancer remission**.

One more important feature for HOT investors should take into account is that **development risk is relatively less for HOT** than other early stage cancer therapeutics. HOT exploits a new cancer-selective delivery and retention mechanism, but is paired with a proven and effective radioisotope (I-131) for therapy. Because, to date, HOT has been shown to reliably and near-universally accumulate in cancer cells and because the therapeutic properties of the iodine-131 are well known, the risk of non-efficacy in human clinical trials is less than that of other cancer therapies at this stage of development. Furthermore, LIGHT PET imaging data is expected to predict efficacy and enable calculation of efficacious doses of HOT for Phase II trials (i.e. LIGHT serves as an ideal and personalized biomarker for HOT). This is important for investors because less development risk means that HOT has a higher probability for success in clinical trials and regulatory approval. Therefore, downside risk is reduced while upside potential remains the same.

Although COLD is in preclinical development, the compound has the potential to become the best-in-class. COLD can be administered by IV versus oral, which will reduce the GI dosing limiting toxicity and increase efficacy due to better toleration at higher levels of drug exposure.

With all these in mind, we think Novelos is undervalued at current price. Currently, Novelos shares are trading at around $0.95 per share, which values the Company at $35 million in market cap, which is a deep discount to its peers. We understand that all the Company's programs are in early stage, cash burn will accelerate in the coming quarters when the Company advances all its three programs. However, we remind investors that both LIGHT and HOT have relatively low development risks compared to other similar cancer programs. We also remind investors that Novelos plans to find a partner for LIGHT after the Phase I/II trial, which could happen as early as in 2013. Such a deal will not only validate the Company's technology, but also will boost the Company's balance sheet with non-dilutive upfront, milestone and royalty.

We are aware of that most small biotech companies of development stage are valued from $50 million to $500 million depending on how advanced the pipeline is and which indications the company is targeting. We think Novelos should be valued between $80 and $150 million at this point. Our price target of $2.5 per share corresponds to a $93 million in market cap.

Catalysts in the next 12-month include:

- LIGHT Phase I/II in Lung Cancer - Initial Data Q2 2012;
- LIGHT Phase I/II in Brain Cancer - Initial Data Q2 2012;
- LIGHT Phase I/II in Other Solid Tumors –Initiation Q2 2012;
- HOT Phase Ib - Ongoing
- HOT Phase IIa in Lung Cancer or Brain Cancer – Initiation Q1 2013
- HOT Phase IIa in Other Solid Tumors – Initiation Q2 2013 H
- Additional Peer Reviewed Publications - Q2 2012

RISKS

Cash Position Is a Concern

As of December 31, 2011, the Company had only $5.5 million in cash and cash equivalents.

In December, 2011, Novelos raised $5.7 million by issuing 10,081,667 units at $0.60 per unit. Each unit consisted of one share of common stock and a warrant to purchase one share of common stock. The warrants have an exercise price of $0.60 per share and a 5-year term.

Current cash can last into 3Q2012. As the Company advances all its three programs, R&D costs will increase.

We believe Novelos needs to tap the capital market very soon and will continue to do so on a regular basis before the Company achieves revenue from product sales or establish any partnership with major pharma or biotech companies. On April 9, 2012, Novelos filed a registration statement on form S-1 for a $10 million public offering.

We remind investors that equity financing will dilute existing shareholder base.

Early Stage Of Development Poses Higher Risks

All Novelos three candidates are in the early stage of development at this point.

Early stage of development poses greater risks as the drug candidate must navigate through the long clinical trials and regulatory review process in order to get into market.

However, the development risk is relatively less for HOT than other early stage cancer therapeutics. HOT exploits a new cancer-selective delivery and retention mechanism, but is paired with a proven and effective radioisotope (I-131) for therapy. Because, to date, HOT has been shown to reliably and near-universally accumulate in cancer cells and because the therapeutic properties of the iodine-131 are well known, the risk of non-efficacy in human clinical trials is less than that of other cancer therapies at this stage of development. This is important for investors because less development risk means that HOT has a higher probability for success in clinical trials and regulatory approval. Therefore, downside risk is reduced while upside potential remains the same. Of course there is no guarantee.

Trading On OTC Market May Be Volatile And Sporadic

There is currently a limited market for the Company's common stock, which is quoted on the over-the-counter market. Trading in stock quoted on over-the-counter market is often thin and characterized by wide fluctuations in trading prices, due to many factors that may have little to do with the Company's operations or business prospects.

Although the Company has received a "QX" designation, the highest tier of the over-the-counter market, the over-the-counter market is not a stock exchange, and trading of securities there is often more

sporadic than the trading of securities listed on a quotation system like NASDAQ or a stock exchange like NYSE. There is no assurance that a sufficient market will develop or remain stable in the stock, in which case it could be difficult for stockholders to resell their stocks. Liquidity may be an issue for institutional investors.

PROJECTED INCOME STATEMENT

	2011A (Dec)					2012E (Dec)					2013E (Dec)	2014E (Dec)	2015E (Dec)	2016E (Dec)
$ in million except per share data	Q1	Q2	Q3	Q4	FYA	Q1E	Q2E	Q3E	Q4E	FYE	FYE	FYE	FYE	FYE
licensing revenue	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$2.50	$5.00	$5.00
Product revenue	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$1.00	$3.50
Total Revenues	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$2.50**	**$6.00**	**$8.50**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	*#DIV/0!*	*140.0%*	*41.7%*
CoGS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Gross Income	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$2.50**	**$6.00**	**$8.50**
Gross Margin	-	-	-	-	-	-	-	-	-	-	*#DIV/0!*	*100.0%*	*100.0%*	*100.0%*
R&D	$0.47	$0.96	$1.01	$1.16	$3.60	$1.10	$1.15	$1.20	$1.30	$4.75	$5.50	$7.00	$8.50	$10.00
% SG&A	-	-	-	-	-	-	-	-	-	-	-	-	-	
SG&A	$0.13	$0.80	$0.91	$0.86	$2.69	$0.87	$0.88	$0.92	$0.95	$3.62	$4.50	$5.00	$5.50	$6.50
% R&D	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other	$0.25	$0.50	$0.00	$0.00	$0.75	$0.25	$0.25	$0.00	$0.00	$0.50	$0.00	$0.00	$0.00	$0.00
% Other	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Operating Income	**($0.9)**	**($2.3)**	**($1.9)**	**($2.0)**	**($7.0)**	**($2.2)**	**($2.3)**	**($2.1)**	**($2.3)**	**($8.9)**	**($10.0)**	**($9.5)**	**($8.0)**	**($8.0)**
Operating Margin	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other Net	$0.1	($0.3)	$0.0	($0.2)	($0.4)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Pre-Tax Income	**($0.7)**	**($2.6)**	**($1.9)**	**($2.2)**	**($7.4)**	**($2.2)**	**($2.3)**	**($2.1)**	**($2.3)**	**($8.9)**	**($10.0)**	**($9.5)**	**($8.0)**	**($8.0)**
Income taxes(benefit)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	-
Reported Net Income	**($0.7)**	**($2.6)**	**($1.9)**	**($2.2)**	**($7.4)**	**($2.2)**	**($2.3)**	**($2.1)**	**($2.3)**	**($8.9)**	**($10.0)**	**($9.5)**	**($8.0)**	**($8.0)**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Net Margin	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Deluted Shares Out	*12.8*	*25.7*	*26.8*	*30.5*	*24.0*	*37.0*	*38.5*	*39.0*	*40.0*	*38.6*	*45.0*	*50.0*	*55.0*	*60.0*
Reported EPS	**($0.06)**	**($0.10)**	**($0.07)**	**($0.07)**	**($0.31)**	**($0.06)**	**($0.06)**	**($0.05)**	**($0.06)**	**($0.23)**	**($0.22)**	**($0.19)**	**($0.15)**	**($0.13)**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-	-	-
One time charge	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*
Non GAAP Net Income	**($0.7)**	**($2.6)**	**($1.9)**	**($2.2)**	**($7.4)**	**($2.2)**	**($2.3)**	**($2.1)**	**($2.3)**	**($8.9)**	**($10.0)**	**($9.5)**	**($8.0)**	**($8.0)**
Non GAAP EPS	**($0.06)**	**($0.10)**	**($0.07)**	**($0.07)**	**($0.31)**	**($0.06)**	**($0.06)**	**($0.05)**	**($0.06)**	**($0.23)**	**($0.22)**	**($0.19)**	**($0.15)**	**($0.13)**

Source: Company filings and Zacks Small Cap Research

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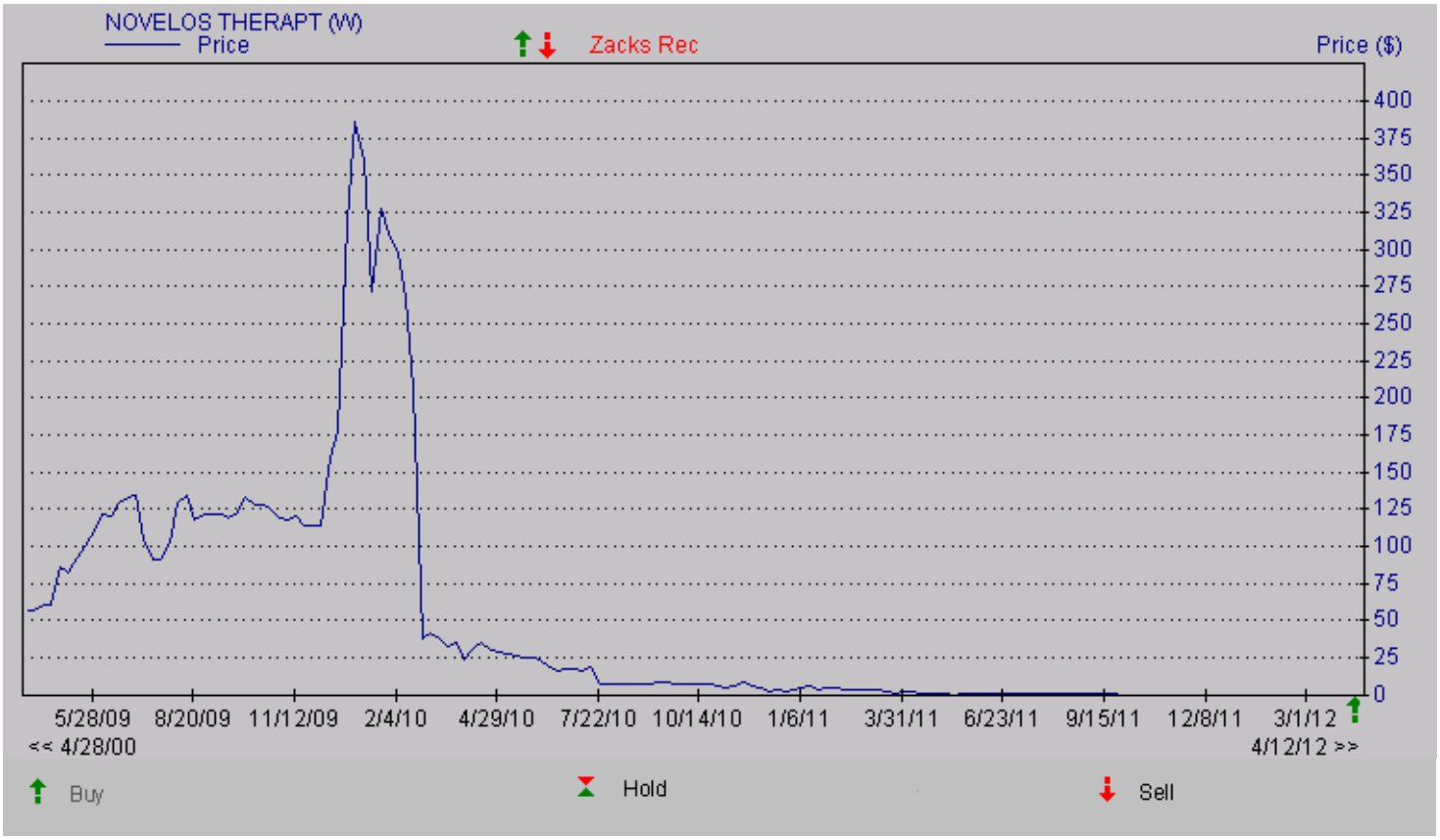
HISTORICAL ZACKS RECOMMENDATIONS



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