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February 21, 2012

Karen Midthun, MD
Director, Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, MD, 20852

Re: Request for FDA Investigation of CellTex Therapeutics Corporation and RNL Bio

Dear Dr. Midthun:

I am writing to request that the Food and Drug Administration initiate an investigation into CellTex Therapeutics Corporation (CellTex) and RNL Bio (also known as RNL Life Science, Inc.). There are at least eight issues that merit investigation by the FDA. Working together in Sugar Land, Texas, these two companies plan to bank stem cells and administer stem cells to their customers for variety of medical conditions. Numerous sources indicate that these companies plan to administer adult stem sells to clients within the next several months. Other news sources state that they already are administering non-FDA approved, clinically unproven stem cells to their customers. Their plans prompt troubling questions concerning patient/client safety, quality of scientific research supporting their proposed business model, and whether the two companies will conform to relevant federal and state laws and regulations. It is unclear how CellTex and RNL Bio intend to address fundamental ethical issues related to protecting patients from risk of harm caused by clinically unproven interventions. It appears that their business plan involves injecting or infusing on a for-profit, commercial basis non-FDA approved adult stem cells into paying customers. This plan conflicts with FDA regulations governing human stem cells.[1] Given their stated intention to commence selling stem cells to customers, I urge the FDA to investigate whether they are compliant with relevant federal and state laws.

RNL Bio engages in some activities that are independent of CellTex. Within Texas, however, RNL Bio and CellTex are tightly integrated. On March 19, 2011, BioLife Stem Cell Corporation, now called CellTex Therapeutics Corporation, entered into a Technology Licensing and Purchase Agreement with RNL BIO.[2] According to the terms of this agreement, CellTex paid $30 million upfront to license and

[1] FDA Warns About Stem Cell Claims. (2012) FDA Consumer Health Information. U.S. Food and Drug Administration. January: 1-2.
[2] Technology Licensing and Purchase Agreement. Available at: http://msnbcmedia.msn.com/i/MSNBC/Sections/TVNews/Nightly%20News/2011%20Stories/Perry_Celltex_PDFs/1_CellTex-RNL%20licensing%20agreement.pdf

purchase RNL Bio's Stem Cell Technology. Subsequent "milestone payments" by CellTex Therapeutics Corporation to RNL Bio are "equal to 20% of the fees received by Licensee from the sale or license of the Stem Cell Technology within the Territory until those milestone payments total $300 million." In turn, RNL Bio has purchased $12.8 million of Preferred Shares of CellTex Therapeutics Corporation Preferred Shares, and committed to acquiring an additional $7.2 million of Preferred Shares.

According to the terms of the licensing agreement, components of the Stem Cell Technology licensed by CellTex include: fat derived autologous stem cell extraction and culture; fat derived autologous stem cell banking, fat derived autologous stem cell treatment, fat derived allogenic stem cell treatment (HLA typing), placenta derived autologous stem cell extraction and culture, placenta derived autologous stem cell banking, placenta derived autologous stem cell treatment, placenta derived allogenic stem cell treatment (HLA typing), iPS technology, and stem cells for cosmetic use. The agreement stipulates that RNL Bio "will, as quickly as possible, assist Licensee in beginning the treatment of patients." Planned initial operating capacity is described as "at least 250 patients per month."

Having reviewed the Celltex Therapeutics/RNL Bio commercial nexus, I proceed to the scientific, legal, and ethical concerns that prompt me to contact you and request that the FDA investigate these companies.

1) I request that the FDA investigate whether there is credible evidence demonstrating that the adult stem cells CellTex and RNL Bio propose administering to their customers are safe and efficacious. I am concerned that CellTex and RNL Bio might be about to begin administering stem cells to customers without an adequate scientific basis for their commercial enterprise. I have been unable to locate a substantial body of peer-reviewed research demonstrating that RNL Bios' "stem cell technologies" are safe, effective, and have a favorable risk-benefit ratio. Have CellTex and RNL Bio provided to the FDA data concerning safety and efficacy of their adult stem cell procedures? If peer-reviewed scientific research demonstrating favorable risk-benefit ratio does not exist, then what scientific, legal, and ethical bases do CellTex and RNL Bio have for selling stem cells to their customers? Upon what legal grounds is CellTex marketing stem cells on a commercial basis rather than operating within the boundaries of a carefully controlled, FDA-compliant clinical trial that informs research participants that they are not receiving established treatment and does not charge them for an experimental, unproven intervention? Setting aside the support CellTex has received from public figures in Texas, it is unclear to me whether there is a significant difference between CellTex RNL Bio Stem Cell Processing Center and other U.S.-based stem cell clinics that the FDA has investigated for possible failure to comply with FDA regulations.

RNL Bio claims to have administered stem cells to over 8000 individuals.[3] However, search of the PubMed database reveals that studies published by RNL Bio researchers use small sample sizes, do not use randomized controlled trial methodology or double blinding in an attempt to eliminate bias from research, do not appear to have undergone IRB review, and involve providing stem cells to individuals

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[3] Tong-hyung, K. (2010). Concerns grow over stem cell therapies. Korea Times. October 26. Available at: http://www.koreatimes.co.kr/www/news/tech/2011/03/133_75215.html.

with significantly different health problems. For example, one study indicates that culture expanded human adipose-derived mesenchymal stem cells were given to ten individuals with "autoimmune hearing loss, multiple sclerosis, polymyotitis, atopic dermatitis, and rheumatoid arthritis."[4] A second study involving RNL Bio researchers focused upon individuals with spinal cord injury. "[5] In this report, stem cells were administered to just eight individuals. The patients had a common type of injury but the sample size is small. If RNL Bio and CellTex have not already provided the FDA with additional studies that are based upon much larger sample sizes, use double blinding and randomized controls, were IRB approved, and conclusively demonstrate safety and efficacy, then I urge you to insist that they submit to you for comprehensive analysis all relevant data from studies involving human research participants and animal study models. Given that CellTex and RNL Bio intend to sell adult stem cells to customers, it is reasonable to expect that there must be substantial clinical data supporting their business model.

2) I request that you investigate reported deaths of individuals who were administered stem cells prepared by RNL Bio. News reports from South Korea indicate that at least two individuals died after receiving stem cells prepared by RNL Bio.[6] One customer reportedly died after receiving treatment in Japan. A second customer is alleged to have died after having stem cells administered in China. A third client claimed that he developed cancer after receiving adult stem cells prepared by RNL Bio. According to Kim Tong-hyung, a reporter for *The Korea Times*, in 2010 former customers claiming that they were "victims of faulty stem cell treatments" disrupted a RNL Bio news conference.[7] Reports allege that RNL Bio processed stem cells without regulatory approval in South Korea, arranged for clients to have non-clinically proven stem cells administered at offshore clinics, allegedly contravened South Korean law by providing non-South Korean FDA approved stem cells to clients at South Korea clinics, and sought to deflect regulatory oversight by cultivating ties to prominent political figures and celebrities.[8,9] (This latter practice has some parallels with recent events in Texas.) As a result of these

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[4] Chan Ra, J. et al. (2011). Stem cell treatment for patients with autoimmune disease by systematic infusion of culture-expanded autologous adipose tissue derived mesenchymal stem cells. Journal of Translational Medicine. 9: 181. Available at: http://www.translational-medicine.com/content/9/1/181.

[5] Chan Ra, J. et al. (2011). Safety of Intravenous Infusion of Human Adipose Tissue-Derived Mesenchymal Stem Cells in Animals and Humans. Stem Cells and Development. 20, 8: 1297-1309. Available at: http://njms.umdnj.edu/gsbs/olc/stemcell2/2011/Oct%2019.pdf.

[6] Tong-hyung, K. (2010). Questions continue over RNLs stem cell handling. Korea Times. November 15. Available at: http://www.koreatimes.co.kr/www/news/tech/2012/01/133_76356.html

[7] Tong-hyung, K. (2010). Concerns grow over stem cell therapies. Korea Times. October 26. Available at: http://www.koreatimes.co.kr/www/news/tech/2011/03/133_75215.html

[8] Ji-sook, B. (2010). Hospitals caught offering illegal stem cell treatments. Korea Times. November 7. Available at: http://www.koreatimes.co.kr/www/news/nation/2010/11/117_75911.html

[9] Tong-hyung, K. (2010). Questions continue over RNLs stem cell handling. Korea Times. November 15. Available at: http://www.koreatimes.co.kr/www/news/tech/2012/01/133_76356.html

allegations, South Korean prosecutors initiated an investigation into RNL Bio. I urge you to contact health authorities in the South Korean Ministry of Health and South Korean Food and Drug Administration and obtain whatever documentation they have concerning reports of clients who died or were injured after receiving stem cells prepared by RNL Bio.

In addition to the domestic investigation initiated by health authorities in South Korea, U.S.-based organization known as International Cellular Medicine Society (ICMS) conducted an investigation of RNL Bio.[10,11] It has come to my attention that Dr. Glenn McGee, the bioethicist who investigated ethical issues related to the reports of two deaths following receipt of stem cells prepared by RNL Bio is now President, Ethics Research Division, at CellTex. I have not seen the full ethics analysis prepared by Dr. Glenn McGee but I can report that it is atypical for a bioethicist to participate in an independent investigation of deaths of patients and then subsequently accept employment at a corporation tied to the business he once investigated. Independent of Dr. McGee's journey from investigating RNL Bio to joining CellTex's senior management team, it appears that the ethics review available on the ICMS website does not adequately address the many ethical issues that need to be confronted when individuals die after receiving clinically unproven interventions. If stem cells prepared by RNL Bio will soon be administered to clients by the CellTex facility in Texas it is imperative that the FDA first investigate whether administration of adult stem cells might already have contributed to the deaths of previous clients of RNL Bio.

3) I request that the FDA review and if necessary test the legal authority of the recent Texas Medical Board draft ruling concerning administration of stem cells. It appears that a recent draft rule approved by The Texas Medical Board will, following publication in *The Texas Register*, a comment period, and a final affirmative vote, enable physicians in Texas to administer non-FDA approved stem cells to patients as "investigational agents."[12] Passage of this rule appears to have occurred with little public debate and despite submissions by scientists concerned that patients will now receive costly, clinically unproven, and possibly unsafe stem cells. According to the Texas Medical Board Rules, "physicians should be allowed a reasonable and responsible degree of latitude in the kinds of therapies they offer their patients. The Board has determined that use of investigational agents constitutes the practice of medicine," and therefore falls within the purview of The Texas Medical Board. The draft rules also state, "Prior to administering or providing of investigational agents, physicians must have their proposed use either included in an FDA/NIH approved protocol/study or approved by an IRB." However, according to the FDA website, "FDA regulates stem cells in the U.S.

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[10] ICMS Conclusions & Recommendations to RNL Bio. Available at: http://www.cellmedicinesociety.org/home/news/latest/330-icms-conclusions-a-requirements-to-rnlbio

[11] Follow-up Ethical Review of RNL Bio. Bio-ethics Investigation. Available at: http://www.cellmedicinesociety.org/home/news/latest/319-follow-up-ethical-review-of-rnl-bio

[12] Texas Medical Board Rules. Texas Administrative Code, Title 22, Part 9. Chapter 198. Standards for Use of Investigational Agents. 198.1-198.4. Available at: http://www.tmb.state.tx.us/rules/proprules_mb.php

to ensure that they are safe and effective for their intended use."[13] I therefore urge you to examine and if required challenge The Texas Medical Board's claim that it is authorized to rule that non-FDA approved stem cells can be administered to humans if an IRB recognized by The Texas Medical Board approves administration of stem cells. It appears to me that the Texas Medical Board has in this particular ruling exceeded its regulatory authority. Within Texas individuals could soon be put at risk of receiving costly stem cell injections or infusions of unknown safety and efficacy.

4) I request that the FDA investigate whether RNL Bio, either in the form of the "parent corporation" or an affiliated RNL Bio company, is already arranging for US citizens to receive non-FDA approved stem cells at clinics located in such countries as China, Japan, and Mexico. RNL Bio reportedly has an office based in Los Angeles. According to news reports, this branch of RNL Bio has sent an estimated 120 clients to China, Japan, and Tijuana, Mexico.[14,15] RNL Bio clients apparently pay $10,000 to $30,000 for services provided by RNL Bio and affiliate clinics. Adult stem cells administered to US citizens are reportedly extracted through liposuction by local, US-based physicians, shipped to a RNL Bio lab in Maryland for processing, sent to Korea to be multiplied, and then sent to clinics outside the U.S. There, the stem cells are administered to RNL Bio clients who travel to these sites. I urge you to investigate whether the Los Angeles and Maryland branches of RNL Bio are in full compliance with laws related to marketing, preparation, and administration of stem cells.

5) I request that the FDA investigate whether CellTex is already administering stem cells to clients. Some individuals assume that stem cells can now be administered to individuals in Texas. To the contrary, at present there is no state-level legal framework in place for permitting CellTex to administer adult stem cells to clients. The rules proposed by the Texas Medical Board are currently in draft form. Furthermore, the FDA has jurisdiction over stem cells administered into humans. However the discrepancy between the draft rule proposed by the Texas Medical Board rule, "Chapter 198. Standards for Use of Investigative Agents," and FDA guidelines governing use of stem cells in both biomedical research and clinical practice is resolved, at present there is no legal or regulatory basis for administering stem cells to patients in Texas. And yet, a blog maintained by a CellTex customer as well as news media reports of Governor Perry's procedure reveal the need to investigate whether some CellTex clients have already received adult stem cells in the absence of any legal, scientific, and ethical framework permitting such activity.[16,17] I am unable to determine from the patient blog that I found

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[13] FDA Warns About Stem Cell Claims. (2012). FDA Consumer Health Information/U.S. Food and Drug Administration. January: 1-2. Available at: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm286155.htm

[14] Lee, A. (2010). Stem Cells Take Root in Koreatown. Los Angeles Business Journal. Available at: http://sabew.org/2011/09/stem-cells-take-root-in-koreatown/

[15] Cyranosk, D. (2010). Korean deaths spark inquiry. Nature. November 23. Available at: http://www.nature.com/news/2010/101123/full/468485a.html

[16] Debbie's Journey. Available at: http://debbiebertrand.blogspot.com/

whether this individual had adult stem cells administered in Texas earlier this month or had her cells banked by CellTex and sought administration of stem cells outside the US. An investigation will resolve where CellTex clients currently are having stem cells administered.

6) I request that the FDA or regulatory authorities with ties to the FDA investigate RNL Bio's efforts to market adult stem cells to prospective customers. Several videos apparently submitted to YouTube by RNL Bio are available for public viewing. These videos consist of testimonials by US citizens who have received stem cells administered by RNL Bio. The videos provide little (or no) information concerning risks. They instead emphasize how clients of RNL Bio were cured or experienced dramatic improvement after receiving adult stem cells. I recommend that FDA investigators determine whether these videos provide an accurate depiction of risks and benefits or instead promulgate an account of adult stem cell interventions that is not supported by clinical data and therefore mislead prospective clients of RNL Bio. Representative videos are available here: http://www.youtube.com/watch?v=i_jqPbTc0Ug; http://www.youtube.com/watch?v=oRFTcCSS_r8&context=C3559c7cADOEgsToPDskLZ8c77AZAblkR-hPUiDygG; and here: http://www.youtube.com/watch?v=oRFTcCSS_r8&context=C3559c7cADOEgsToPDskLZ8c77AZAblkR-hPUiDygG.

7) I request that the FDA investigate how CellTex and RNL Bio propose to address fundamental questions concerning informed consent and adequacy of protections for individuals receiving non-FDA-approved stem cells. Once medical interventions are determined to be safe and effective and are introduced into the practice of clinical medicine, patients must be provided information that enables them to make informed choices. Research subjects considering participation in clinical trials also must make informed decisions about whether to participate. Whether or not CellTex and RNL Bio plan to frame the services they market as clinical medicine or medical research is unclear. It seems to me that there is no basis for characterizing administration of adult stem cells as an element of established clinical medicine rather than research that ought to be conducted within the context of FDA-approved clinical trials. However these two companies define what they are doing, I have been unable to obtain publicly accessible information concerning how Celltex and RNL Bio propose to describe to clients risks and benefits associated with receiving stem cells. I urge you to investigate whether it has been conclusively demonstrated that there is an adequate risk-benefit ratio for administration of adult stem cells into humans, whether sufficient data from both clinical trials in humans as well as animal studies exist, and, if stem cells are to soon be administered to CellTex customers, what information about risks and benefits will be provided to clients. If there is too little clinical trial data available to make credible statements about risks and benefits, it is unclear to me how it will be possible for CellTex and RNL Bio to adequately describe risks and benefits associated with whatever services they provide and ensure that clients are making informed, evidence-based choices. If their clients "consent" to stem cell interventions without being given meaningful information they could be exposed to an unacceptably high level of risk. The commercial nature of this enterprise is another cause for concern. Payment for provision of adult stem cells risks conveying the impression

[17] Ramshaw, E. (2011). Perry's Adult Stem Cell Treatment Was Doctor's First Attempt. The Texas Tribune. August 4. Available at: http://www.texastribune.org/texas-people/rick-perry/perrys-stem-cell-treatment-was-doctors-first-attem/

that CellTex and RNL Bio are marketing established clinical therapies. If the FDA has grounds for allowing CellTex and RNL Bio to proceed with provision of adult stem cells in the context of a clinical trial then stem cells should be administered without charge to individuals providing informed consent and agreeing to enroll in clinical studies as voluntary, informed research participants.

8) I request that you investigate whether Dr. Stanley Jones was in compliance with FDA regulations when he administered adult stem cells to his patient, Governor Rick Perry. Before the Texas Medical Board issued a draft ruling February 10, 2012, Dr. Jones, Vice President and Chief Medical Officer of CellTex, reportedly administered adult stem cells to Governor Perry.[18] It is unclear what scientific, clinical, legal, and ethical justification Dr. Jones had for administering non-FDA approved stem cells.

Acknowledging the mixture of hope and desperation that sometimes drives individuals to consider receiving stem cell interventions—whether in Texas or by traveling to clinics located in such countries as China, Costa Rica, Dominican Republic, India, Mexico, Russia, and Ukraine—by now there are numerous reports describing cases in which individuals have died or been harmed after receiving clinically unproven, non-FDA approved stem cells.[19,20] I urge the FDA to protect ill and injured persons from risk of harm by investigating whether CellTex and RNL Bio are in full compliance with U.S. laws and regulations, scientific norms, and ethical standards governing provision of stem cells to humans. Initiating an investigation before the CellTex facility fully "scales-up" and many clients begin receiving adult stem cells is far preferable to waiting and taking action only after stem cell recipients are harmed. I recommend that the FDA act now and determine whether CellTex Therapeutics and RNL Bio are in compliance with FDA guidelines as these companies proceed toward administering to their customers adult stem cells and other stem cells for illnesses, injuries, and cosmetic purposes.

CellTex is based at 2401 Fountain View Drive, Houston, TX 77057-4827. The phone number for CellTex is 713-590-1000. CellTex executives include **Mr. David G. Eller**, Chairman and Chief Executive Officer; **Dr. Stanley Jones**, Vice President and Chief Medical Officer, **Dr. Glenn McGee**, President of Ethics and Strategic Initiatives, and **Donna Lee**, Vice President. RNL Bio is a South Korean company that is registered or has applied for registration as a Foreign-For-Profit corporation in the State of Texas. Within the U.S. the principal office of RNL BIO is 20271 Goldenrod Lane, Germantown, MD, USA 20876. The phone number for RNL Bio is 301-515-5114. **Dr. Jeong-Chan Ra**, **Jungwoo Jung**, and **Jin Han Hong** are Company Directors. I hope you receive full cooperation of company executives at both CellTex and RNL Bio should you conclude that some or all of the concerns that I have noted warrant investigation by the FDA.

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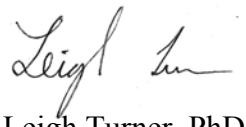
[18] Ramshaw, E. (2011). Perry's Surgery Included Experimental Stem Cell Therapy. The Texas Tribune. August 3. Available at: http://www.texastribune.org/texas-people/rick-perry/perrys-surgery-included-experimental-stem-cell-the/

[19] Sipp, D. (2011). Stem cell stratagems in alternative medicine. Regen. Med. 6, 3: 407-414. Available at: http://www.futuremedicine.com/doi/pdf/10.2217/rme.11.13

[20] Nagy, A., Quaggin, S. (2010). Stem Cell Therapy for the Kidney: A Cautionary Tale. J. Am. Soc. Nephrol. 21: 1070-1072. Available at: http://jasn.asnjournals.org/content/21/7/1070.short

Please feel welcome to contact me if you have any questions related to my request for FDA investigation of CellTex and RNL Bio's plan to administer stem cells to customers, wish to receive additional documentation, or want me to further explain why I believe the FDA needs to investigate CellTex Therapeutics and RNL Bio and establish whether their plan to administer stem cells to clients falls within the scope of federal law, peer-reviewed scientific research, evidence-based medicine, and ethical treatment of patients. Thank you for considering this request.

Yours sincerely,



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