CellVi's AdviCell™ Conditioned Media:

Why Is This Currently The Best Scientifically Proven Product Of Its Kind?

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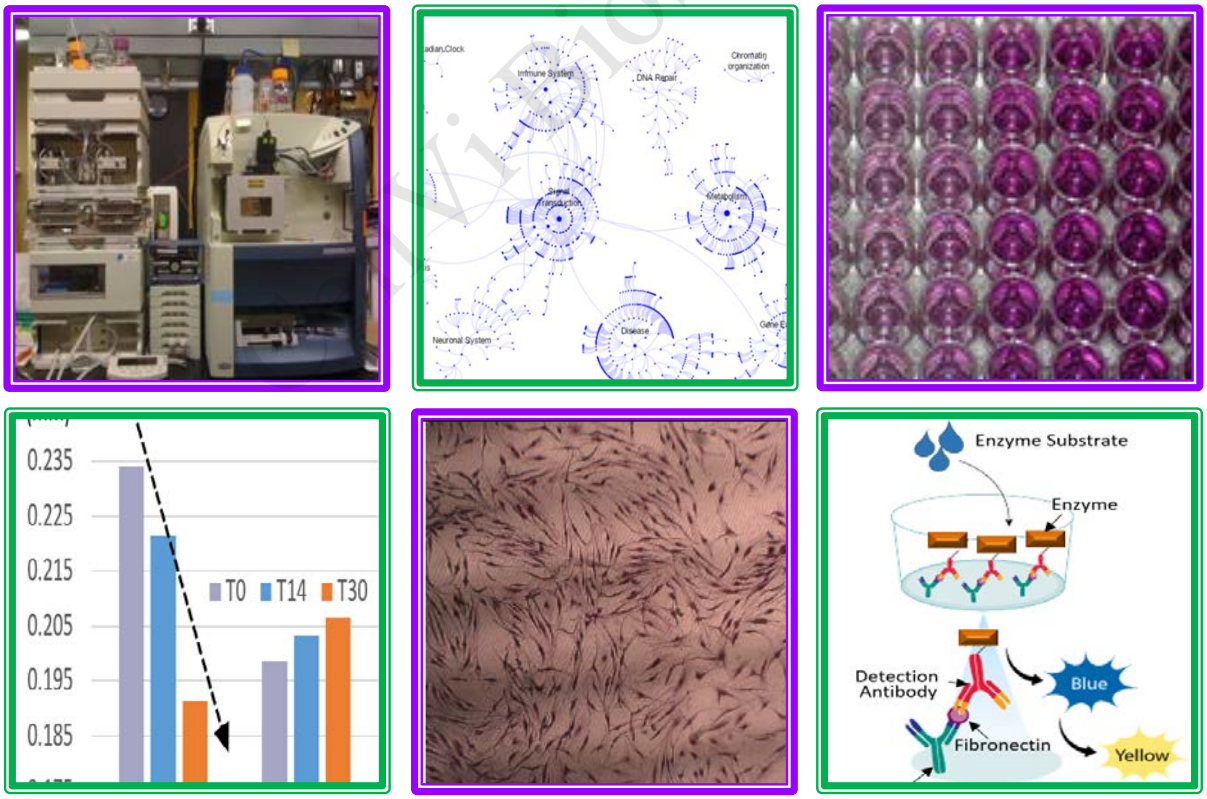

CellVi BIOSCIENCE

EXECUTIVE SUMMARY

Human Cell Conditioned Media (conditioned media hereafter) consist of a complete ensemble of the native proteins that certain skin-important human cells produce while growing in their culture media. Among cosmetic raw materials thus far developed, they are the best 'cut-to-the-chase' source capable of improving the target site. This science is now emerging as the next wave of performance for skin care technology. Still in its infancy, however, just like many other new sensations in natural sciences, there is a large yet-to-be-filled comfort zone. The skin care industry remains optimistic, but notably cautious about the conditioned media derived products, especially in light of their incomplete biological profiles, longer-term safety, and quality control & assurance issues. Here we present CellVi's conditioned media, AdviCell™ (AdviCell hereafter), and why it makes the best scientifically characterized and proven product of its kind so far available in the market. This paper demonstrates 1) AdviCell's entire identifications of protein contents, 2) their associated cellular/molecular mechanisms via protein pathway analysis, 3) experimental evidence regarding how it rejuvenates aged human skin cells through its growth controlling properties, and 4) considerable clinical improvements, in anti-wrinkle efficacy and skin firmness & complexion, manifested within 30 days' application by the AdviCell conditioned media itself as the sole ingredient. In addition, protein markers are being developed for AdviCell to be manufactured under consistently superior quality control and assurance.

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I. INTRODUCTION

A series of *bona fide* biochemical reactions take place inside our body all the time. As our life expectancy has increased thanks to significant advances in modern biomedical tools, so has anti-aging research in the bioscience laboratory. Tremendous efforts are underway to slow down or reverse body's aging process by targeting the pertinent molecular interactions occurring at a cellular level. It was only a natural progression that the cosmetic industry turned to human cellular source materials to combat aging skin over the past decade. A myriad of so called "bio-cosmetics" have been expressed into this market. Such ingredients include plant stem cells, recombinant/synthesized growth factors, one's own human stem cells, and a whole orchestra of proteins secreted from specialized skin-relevant cells (conditioned media). Each source is boasting its own Pro's while softening down inherent Con's of the respective biological property.

Comparing pros and cons of the different biologic sources is outside the scope of the present paper and warrants a comprehensive analysis dedicated to a separate manuscript. However, in the eyes of cellular molecular biologists who profoundly understand our body's cellular physiology at a molecular level, use of the conditioned media is believed to be the most biologically sensible, safest, and most economical approach. It can most effectively support our aging skin cells with what they need to clock back time at a molecular level. It provides a self-sufficient micro-environment where our skin cells can auto-pilot maintenance of their youthful healthy state, like a fountain continuously replenishing much needed nutrients and water to keep cells from aging. Conditioned media can be generated from various cell type sources. Currently available media in the market are mostly made from neo-natal fibroblasts, adult mesenchymal stem cells derived from adipocyte, bone marrow, or placenta.

Each different source produces respectively valuable sets of proteins best reflective of the cell origin and function. Our AdviCell™ (AdviCell hereafter) conditioned media was developed after elaborate lab research by CellVi's experienced cell biologists. Based on the experimental processes and analyses presented in the pages 5-9 of this paper, AdviCell was created using proprietary culturing methods and blend ratios of multiple cell sources from the above list to contain the most effective/beneficial protein contents in the safest manner (with built in autocrine growth controlling mode). This paper will present how AdviCell overcame the various concerns with existing conditioned media derived skin care products (see the below Problem Statement) to be the best scientifically proven in terms of its protein contents, longer-term safety feature, improved QC/QA measure, and clinical testing result.

II. BACKGROUND/PROBLEM STATEMENT:

Concerns with the Existing Conditioned Media Derived Skin Care Products

1) Lack of complete list of the protein contents:
This is a concern for 'partially unknowns'. It is well appreciated that one of the best advantages with conditioned media is its collective nature of multiple different proteins. Most of existing conditioned media name a handful of important growth factors and cytokines present in their soup with a vague total estimate of "up to 150 proteins" or "over 200 proteins". Then what are the rest of proteins in the mixture? Its complete ingredient list has not been thoroughly identified yet. One may be wondering "what if some unwanted/harmful proteins are also present?". Also, this lack of complete list has hampered an accurate and comprehensive analysis of exactly what molecular mechanisms the conditioned media operate in our skin tissue.

2) Longer-term health safety, in particular concern for cancer development:
Understandably, the end users may be concerned "what if those growth promoting proteins present in conditioned media work too well beyond the boundary as to lead to uncontrolled cell growth, i.e. cancer?".

3) Perplexity in choice of cell type source:
Currently, respective conditioned media manufacturers biologically rationalize why their cell source type is the most beneficial to the skin, i.e. fibroblast vs. adult stem cell; adipocyte vs. bone marrow derived, etc. Some go to the extent of claiming why others' cell sources can be not only inferior but also can be dangerous to the human body.

4) Lack of quality control & assurance measure:
Compared to synthetic bio-molecules or chemical based ingredients, native (functionally active) protein contents in conditioned media is considerably more challenging in terms of quantifying their intact protein contents to ensure consistent batch-to-batch quality control.

5) Is added value improvement purely contributed from conditioned media?
Conditioned media as a raw material is incorporated in formulation toward value-added finished skin care products. Yet clinical testing is performed largely using the final products containing many other active ingredients. Then how can we truly discern how much share of improvement is contributed purely by conditioned media? For good reasons, cosmetics containing biologic moiety such as conditioned media are much more costly to compensate for expensive skillful labors and/or extra arduous process to upkeep biological functional activity. Can this enormous undertaking be just commercial hype for the sophisticated sounding new products which are not truthfully adding much improvement proportional to consumers' spending?

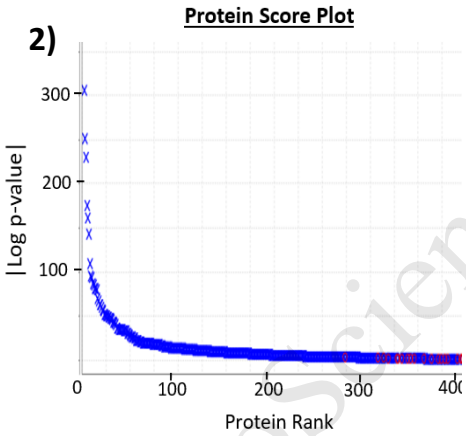
III. SOLUTION: How Did AdviCell™ Improve the Prior Art?

A. AdviCell Contains the Full Array of Proteins/Peptides Identified to Promote Skin Care.

In order to detect the entire array of proteins and peptides present in AdviCell, Liquid Chromatography-Mass Spectrometry (LC-Masspec) was performed at Stanford University Proteomics Core Facility (Stanford, CA). This is a cutting-edge technology for protein identification from a small sample solution. All the proteins contained in AdviCell were digested to smaller sized peptides which then were purified, concentrated, and applied to the mass analyzer. Multiply charged peptides were selected by abundance for sequencing by the mass spectrometer. The characteristic pattern of peptides is used for the identification of the protein against the Protein Library database. For details, refer to https://mass-spec.stanford.edu/protein-identification

1)

2)



1) Micromass Quattro Premier triple quadrupole, Agilent 1100 HPLC-MS was used in a peptide centric (bottom up) approach to identify the amino acid sequences of the entire peptides present in AdviCell; **2)** Protein Score Plot: Each X mark represents a distinctive protein and it is displayed on the plot by the Log of Probability score;

3)

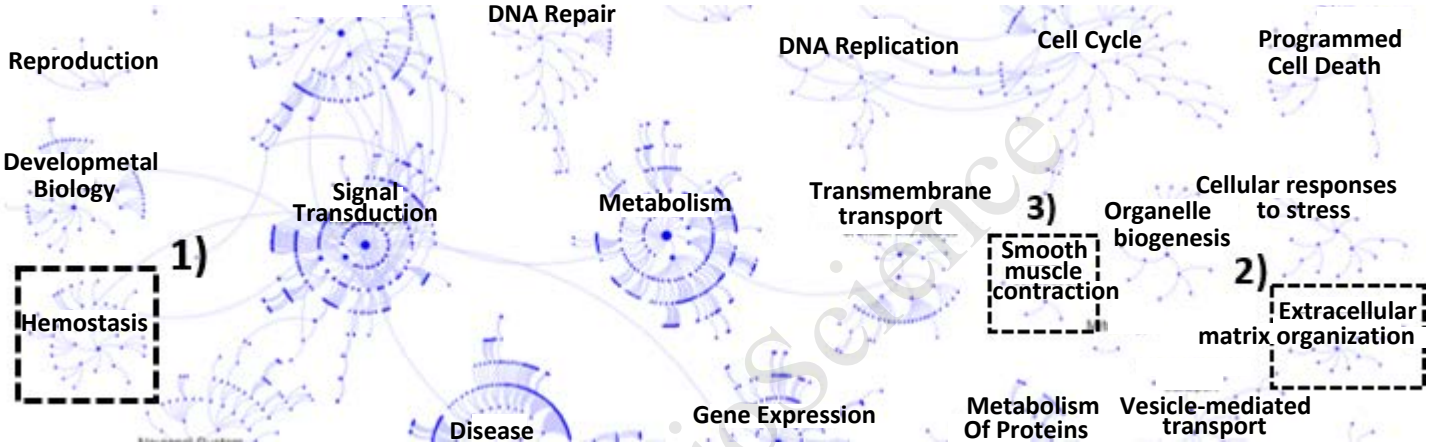
Protein Rank	Description	|Log Prob|	Best |Log Prob|	Best score	Total Intensity	# of spectra	# AA's in protein	Protein DB number
1	>sp|P02751|FINC_HUMAN Fibronectin OS=Homo sapiens GN=FN1 PE=1 SV=4	305.78	13.98	828.60	46347761.0	83	2386	11503
2	>sp|P02751-3|FINC_HUMAN Isoform 3 of Fibronectin OS=Homo sapiens GN=FN1							
3	>sp|P02452|CO1A1_HUMAN Collagen alpha-1(I) chain OS=Homo sapiens GN=COL1A1 PE=1 SV=5	250.84	15.33	900.40	16616886.6	59	1464	6653
4	>sp|P08123|CO1A2_HUMAN Collagen alpha-2(I) chain OS=Homo sapiens GN=COL1A2 PE=1 SV=7	229.79	13.84	866.20	11902934.4	59	1366	6654
5	>sp|P07996|TSP1_HUMAN Thrombospondin-1 OS=Homo sapiens GN=THBS1 PE=1 SV=2	175.39	9.95	680.70	43638852.1	60	1170	32542
6	>sp|P60709|ACTB_HUMAN Actin, cytoplasmic 1 OS=Homo sapiens GN=ACTB PE=1 SV=1	161.17	13.66	895.20	31605011.7	42	375	677
6	>sp|P63261|ACTG_HUMAN Actin, cytoplasmic 2 OS=Homo sapiens GN=ACTG1 PE=1 SV=1							
7	>sp|Q9Y490|TLN1_HUMAN Talin-1 OS=Homo sapiens GN=TLN1 PE=1 SV=3	142.91	10.01	682.80	14696290.6	27	2541	31311
⋮								
162	>sp|P67936-2|TPM4_HUMAN Isoform 2 of Tropomyosin alpha-4 chain OS=Homo sapiens GN=TPM4							
163	>sp|P23526|SAHH_HUMAN Adenosylhomocysteinase OS=Homo sapiens GN=AHCY PE=1 SV=4	8.06	6.25	535.50	1685049.9	3	432	27601
164	>sp|Q12931|TRAP1_HUMAN Heat shock protein 75 kDa, mitochondrial OS=Homo sapiens GN=TRAP1 PE=1 S	7.93	7.96	581.60	449058.6	1	704	32155
165	>sp|P12107|COBA1_HUMAN Collagen alpha-1(XI) chain OS=Homo sapiens GN=COL11A1 PE=1 SV=4	7.91	4.63	401.60	1002632.1	5	1806	6712
165	>sp|P12107-2|COBA1_HUMAN Isoform B of Collagen alpha-1(XI) chain OS=Homo sapiens GN=COL11A1							
165	>sp|P12107-3|COBA1_HUMAN Isoform C of Collagen alpha-1(XI) chain OS=Homo sapiens GN=COL11A1							
⋮								
334	>sp|P55263-2|ADK_HUMAN Isoform Short of Adenosine kinase OS=Homo sapiens GN=ADK	2.20	2.21	325.80	1542290.4	3	345	860
335	>sp|O43505|B3GN1_HUMAN N-acetyllactosaminide beta-1,3-N-acetylglucosaminyltransferase OS=Homo sap	2.17	2.19	275.60	236872.3	1	415	2674
336	>sp|Q15063-3|POSTN_HUMAN Isoform 3 of Periostin OS=Homo sapiens GN=POSTN	2.17	2.18	400.30	580776.5	2	781	24059
337	>sp|Q03181|PPARD_HUMAN Peroxisome proliferator-activated receptor delta OS=Homo sapiens GN=PPARD	2.13	2.15	404.30	230377.5	1	441	24156
338	>sp|Q93099|HGD_HUMAN Homogentisate 1,2-dioxygenase OS=Homo sapiens GN=HGD PE=1 SV=2	2.09	2.01	323.50	428118.7	2	445	13733
339	>Reverse >sp|A2RRP1|NBAS_HUMAN Neuroblastoma-amplified sequence OS=Homo sapiens GN=NBAS PE=1	2.07	2.14	362.00	1397552.9	5	2371	55885
339	>Reverse >sp|A2RRP1-2|NBAS_HUMAN Isoform 2 of Neuroblastoma-amplified sequence OS=Homo sapiens (							
340	>sp|O76074|PDE5A_HUMAN cGMP-specific 3',5'-cyclic phosphodiesterase OS=Homo sapiens GN=PDE5A PE=1	2.06	2.09	379.00	160965.2	1	875	22921
340	>sp|O76074-2|PDE5A_HUMAN Isoform PDE5A2 of cGMP-specific 3',5'-cyclic phosphodiesterase OS=Homo sap							
⋮								

KEY FINDING 3) A representative list of over 540 proteins identified to be present in AdviCell. Protein rank listed in the first column represents a relative abundance level of each protein/peptide identified, the lower numbers being the higher concentration. As expected, a majority of proteins and peptides detected are involved in various cellular functions to promote skin cell growth, skin reconstruction & regeneration, and rejuvenation of aging cells via molecular mechanisms presented in page 6.

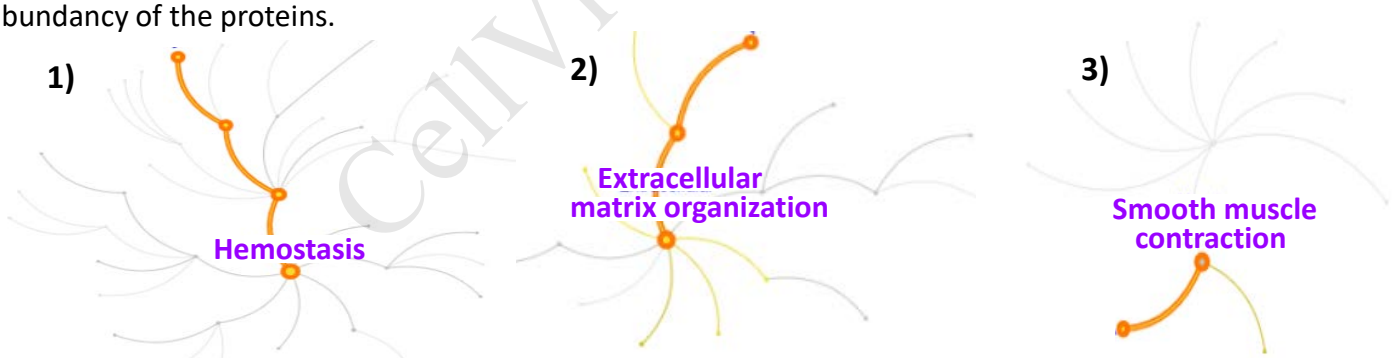
III. SOLUTION: How Did AdviCell™ Improve the Prior Art?

B. AdviCell Functions in Skin Repair, Extracellular Matrix, and Smooth Muscle Contraction Pathways.

Identification of a sufficient number of proteins (>540) present in the conditioned media system enabled us to perform protein pathway analysis to elucidate exactly by what kind of cellular/molecular functional mechanisms AdviCell contributes in improving skin condition. www.reactome.org (A Curated Pathway Database, Reactome V57). The below schematic diagram shows how all the human protein species thus far discovered are organized into groups performing related cellular functions. Names written in the center of each circular array demonstrate master functions that the cellular proteins carry out in a hierarchical manner. Multi layers of the functional sub-groups are formed illustrating profound depth and complexity of a total collection of human proteins interacting among each other in our cells.



When we applied approx. 540 proteins identified from AdviCell in the Protein Pathway software, the following three functional groups received the highest scores. The branches highlighted in orange/yellow colors are the particular sub-groups the AdviCell proteins are found (color intensity proportional to the abundancy of the proteins.

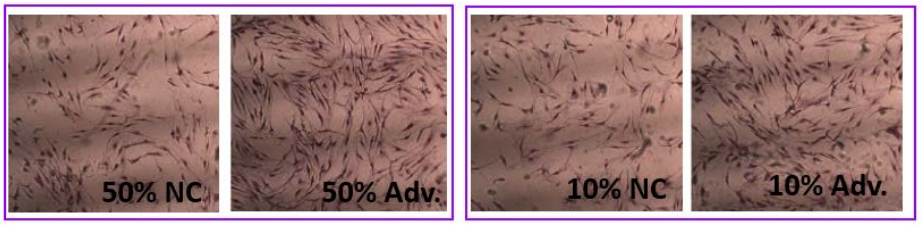


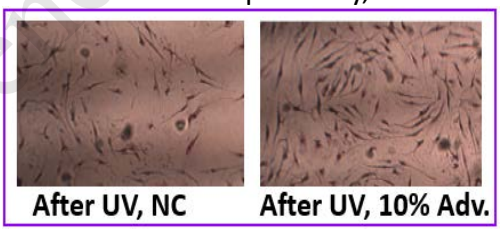
KEY FINDING **1) Hemostasis** is a process which causes bleeding to stop and is the first step of the **wound healing** mechanism including platelet activation, signaling, and degranulation. Considering aging skin is a form of wound, the rejuvenation effects of AdviCell is explained by the most abundant presence of the beneficial proteins for healing wounds; **2) Extracellular matrix organization** proteins give our skin dermis firm structural support and intact functions. Collagens, elastin, fibronectin, actin, and many others belong to this group. AdviCell's anti-wrinkle effect can be best explained by its rich concentration of almost all the extracellular matrix proteins found in our skin; **3) Smooth Muscle contraction** proteins are essential for giving our skin elasticity and anti-aging effects.

III. SOLUTION: How Did AdviCell™ Improve the Prior Art?

C. AdviCell Rejuvenates Aged Human Skin Cells.

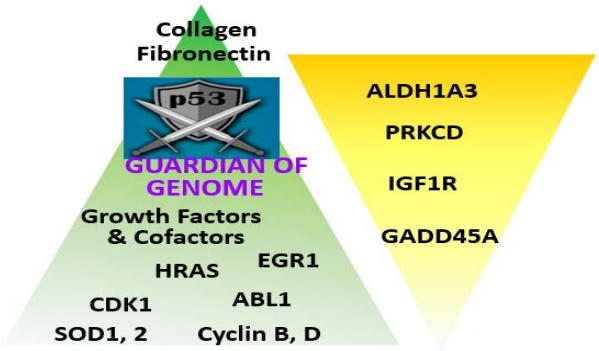
In order to visually demonstrate AdviCell's cellular 'rescue action' - how it rejuvenates aged and stressed/injured human skin cells, adult human dermal fibroblast cells were nutritiously deprived for 6 days (removal of growth factors from their culture media). Then cells were divided to two groups to compare the growth profiles in their regular media (**N**egative **C**ontrol) vs. 50% AdviCell (Adv.). To determine whether AdviCell improves cell rejuvenation in a dose dependent manner (direct evidence that AdviCell is indeed a benefactor), the second set of the cells were grown in parallel in the same negative control media vs. 10% AdviCell. After 24 hours of growth, cells were photographed by inverted fluorescence microscopy and attached high resolution video camera. Cell numbers were quantified by microplate spectrophotometer. The above pictures demonstrate 50% AdviCell treatment helped the stressed cells to bounce back quicker to grow more robust and healthier in better proliferation than the negative control cells. Importantly, the rejuvenation rate was proportional to the AdviCell concentration (50% vs. 10%) suggesting direct role of AdviCell in cell revival. Similarly, AdviCell (Adv.) restored adult human fibroblast cells irradiated by uv light (mimicking aged, wounded cells) to the healthy growing state more effectively than its negative control (NC) counterpart (no AdviCell added).





D. AdviCell Expresses Genes Related to Cell Regeneration in a Growth Regulatory Manner.

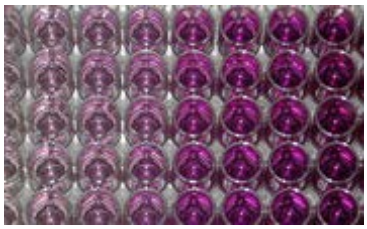
Next, we wanted to investigate when those stressed cells rejuvenate with the help of AdviCell, what kind of genes/proteins are being produced within their own cell system. This experiment was to ask a question "when AdviCell containing cosmetic is applied to our skin, how do our own cells respond at a molecular level? To this end, we analyzed gene expression changes when the cells are treated with 50% AdviCell compared with the cells grown in the absence of AdviCell (the same cell pair as above). The two triangles here illustrate representative genes found to be increased (upright triangle) or decreased (upside down), respectively, by AdviCell treatment. Genes inside each triangle are listed by their relative fold increase/decrease rank, the higher on the list the greater fold change. Expectedly, proteins of cosmetic relevance, such as type I collagen and fibronectin were increased at the highest fold. Also increased were genes which function in protecting cells from "unhealthy dying (senescence)", such as cell growth promoters (ABL1, CCND1, CDK1, HRAS) and antioxidant defenders (SOD1, SOD2). Most interestingly, in this remarkably pro-regenerative response, the well-known Guardian of Genome, p53 tumor suppressor gene, was most consistently increased, while IGF1R and PRKCD tumor promoters were constantly decreased. This finding suggests AdviCell renders a built-in auto- growth controlling/regulating mechanism in the cell. Importantly, the genes found to be regulated by AdviCell in our study are closely correlated to those protein functional groups identified in our Pathway Analysis (page 5).



III. SOLUTION: How Did AdviCell™ Improve the Prior Art?

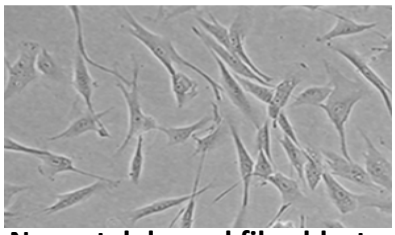
E. AdviCell Upregulates Normal Skin Cell Growth While Slowing Melanoma (Skin Cancer) Cells.

After we gained preliminary evidence that AdviCell renders a self-regulatory growth controlling measure to their recipient cells, we wanted to compare the growth promoting effects of AdviCell on skin cancer cells vs. normal skin cells. Cancer cells by their nature grow considerably faster, i.e. out of control even in compromised nutrient and spatial conditions, not only in our body but also in the tissue culture dish in the lab.

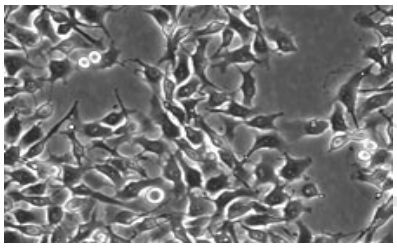


MTT assay: Increasing amounts of cells demonstrate increased purple coloring.

Given the experimental data AdviCell promotes fast and robust regenerative growth in normal skin cells (shown in the **C.** section), would it then confer cancer cells (already at a high speed gear) even more aggressive growth? To answer this question, we compared AdviCell-induced growth pattern of the B16F10 murine melanoma cells vs. neonatal human dermal fibroblasts. Both cells started at an equal number (3,000 cells/well) in the same common tissue culture media. After 24h, AdviCell was added at 50% to each test sample ("0" time point, T0) to compare how much each has grown within next 48 hours ("48h" time point, T48), i.e. % Growth comparison. Cell viability and proliferation was measured by MTT assay which is a commonly used technique to determine cell metabolic activity by microplate spectrophotometer.



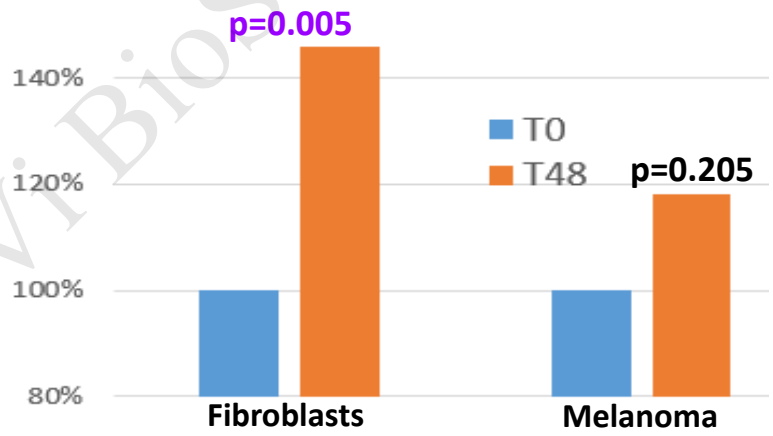
Neonatal dermal fibroblasts



B16F10 skin cancer cells

Top picture shows typical growth appearance of the 'normal' fibroblasts, well differentiated and growing in a regulated mode; Bottom picture shows typical growth profile of cancer cells, growing aggressively out-of-control mode.

% Growth Comparison Bar Graph



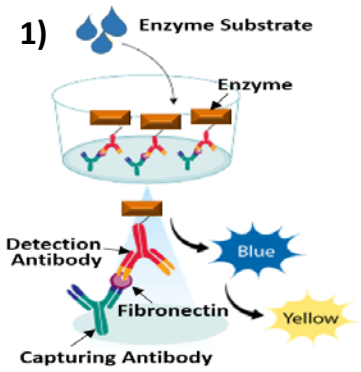
Normal cells (neonatal dermal fibroblasts) and melanoma skin cancer cells demonstrated different growth rates within 48 hour time period. According to the statistical analysis (paired t-test), the cell number increase in fibroblasts displayed statistically significant growth, at p=0.005, while the growth increase in melanoma cells (p=0.205) did not reach statistical significance, and was considerably lower than expected for typical cancer cells growing in their regular environment. This data confirms the hypothesis that AdviCell renders cells regenerative capability towards an anti-aging mode, without promoting unwanted/uncontrolled cell growth burst. We theorize that this controlled growth in cancer cells is contributed by higher expression of the P53 tumor suppressor gene induced by AdviCell (page 7).

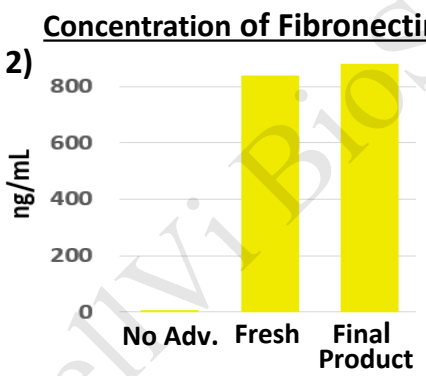
III. SOLUTION: How Did AdviCell™ Improve the Prior Art?

F. AdviCell Enhances Quality Control & Assurance By Its Protein/Peptide Markers In Development.

Achieving a consistent quality and quantity, in terms of active ingredient (protein) stability and constant functional activity, purity, and the same amount of proteins per sample, is especially challenging when it comes to hard-core biological raw material such as conditioned media. There is a great chance for batch-to-batch variability thus hampering consistent quality control and assurance. This is especially true due to the laborious processes of growing cells at tissue culture environment which can lead to great discrepancy in output conditions as well as extra strenuous storage condition of the biological material. How can we assure a consistent and long shelf-life of conditioned media derived cosmetic products? In order to tackle this issue, cell biologists at CellVi have been developing protein marker assay system. That is, a methodology for quantifying a set of key protein components present in AdviCell is being developed using a technique called ELISA (Enzyme-Linked ImmunoSorbent) assay. This protein quantification method has the detection sensitivity down to pg/mL of proteins present in a solution. Example shown here uses an enzyme selected to specifically detect fibronectin protein. Fibronectin is one of the essential components of the extracellular matrix underlying skin dermis and is abundantly present in AdviCell.

CellVi's AdviCell Quality/Quantity Control Protein Marker Development: The 96 well plate ELISA assay enables us to compare 96 sample size simultaneously.





1) ELISA assay principal: a single fibronectin protein molecule is detected by the two types of Antibodies which only bind to fibronectin. Then, the enzyme attached in the detection antibody will react with its specific substrate (blue) to induce color change to yellow; **2)** This bar graph shows concentrations of the fibronectin protein marker. We can measure the protein concentration in AdviCell (Adv.) samples prepared at different time points and/or at different states/stages. Shown here is the fibronectin content in the freshly harvested AdviCell conditioned media from tissue culture flasks (Fresh) vs. formulated into the "Final Product" after stored at -80°C for a number of months, thawed, and added with the preservative, then kept at 4°C for months (for a shelf life measure). We confirmed that the protein marker quantity and quality remains stable throughout the series of laboratory processes. We are currently developing a set of protein markers to be able to establish and maintain consistent QC/QA measures. (No Adv.=regular tissue culture growth media, negative control)

G. AdviCell is a Blend of Multiple Cell Type Sources Developed for the Most Optimal Skin Care Outcomes.

At CellVi, after endeavoring repeated analysis of molecular/cellular experiments presented **A.** through **F.** above to accomplish the most optimal recipe of conditioned media, "AdviCell" was created to have a proprietary blend ratio of multiple cell type sources and their respective culture method uniquely developed at CellVi laboratory. AdviCell was generated to consist of the most effective and proficient assembly of intact protein molecules which has the best rejuvenation capacity with a demonstrated safe growth regulatory feature.

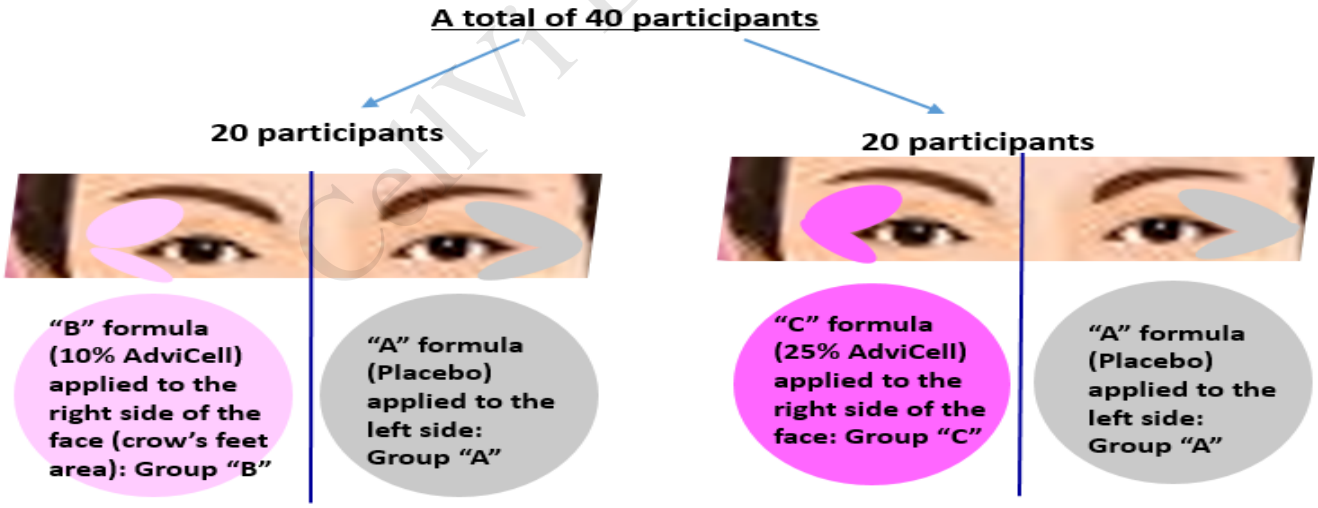
III. SOLUTION: How Did AdviCell™ Improve the Prior Art?

H. AdviCell Improves Various Skin Conditions in Clinical Test Using It as a Sole Active Ingredient.

1) Clinical Test Design

It has been well recognized that skin care products containing conditioned media in general as one of the active ingredients have shown excellent improvements for end-users' skin condition. In fact, in our unofficial clinical test setting in which final formulated skin care products made with AdviCell were given out as a sample to a handful of industry experts/beauticians as well as a large number of lay consumers, we had received overwhelmingly positive responses and zealous enthusiasm to acquire more to continuously apply. Therefore, we set out to design our clinical testing with the focus of determining how much of the generally well-appreciated improvement by conditioned media cosmetics is actually contributed by conditioned media itself, independent of many other active ingredients present in the final product. In addition we wanted to ask how soon conditioned media itself is effectively contributing to the anti-aging effects of its commercially bound products. Lastly we wanted to observe AdviCell dose dependent effects by including the two concentrations for test products, 10% vs. 25%. To this end we formulated our testing product "B" and "C" vs. Placebo "A" according to the following compositions.

Placebo used as a negative control only consisted of basic filler materials such as hydroxethyl cellulose, ethylhexyl glycerine, etc. "B" and "C" formulas were exactly the same composition as placebo except containing 10% and 25% AdviCell at final volume concentrations respectively.



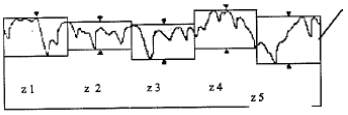
This clinical study was performed at Abich Laboratory, Milan, Italy: a total of 40 healthy female participants, aged between 35 and 60 years old and showing wrinkles, lack of skin firmness and dull skin complexion, were identified from Abich Clinical Study Center database. Respective formulas given out to participants in a blind-folded manner were applied twice a day. Participants were measured for anti-wrinkle efficacy (R*z*), Skin firmness (R*0*), and skin complexion (ΔE) at **Days 0, 14, and 30** (**T0, T14, and T30** time points respectively).

III. SOLUTION: How Did AdviCell™ Improve the Prior Art?

H. AdviCell Improves Various Skin Conditions in Clinical Test Using It as a Sole Active Ingredient.

2) Anti-Wrinkle Efficacy

Rz represents the average of the roughness (skin trough/wrinkle) measured from 5 succeeding segments of the same length. In contrast to the other profile roughness parameters, Rz is not that much influenced by artifacts based on calculating the average. **The higher the Rz value is, the deeper wrinkles are.**



$$Rz = \frac{z1 + z2 + z3 + z4 + z5}{5}$$

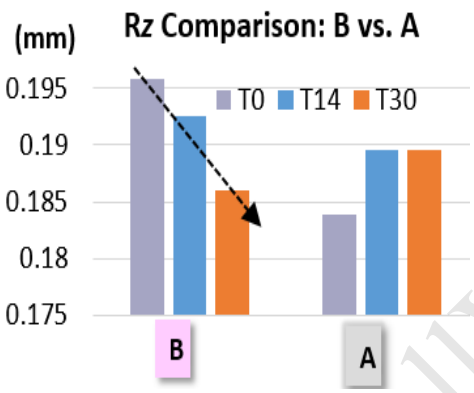
The equipment used for this measurement was Derma TOP-blue di Eotech. (see detail procedures at http://eotech-sa.com/Life-science/Systems/DermaTOP-HE/Products/t1/r9/i111)

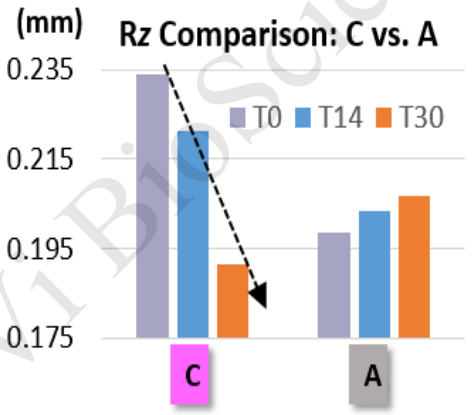
Time	Mean Rz (mm)	
	B	A
T0	0.1958	0.1839
T14	0.1925	0.1896
T30	0.1860	0.1896

Time	% variations		p-value	
	B	A	B	A
T14 vs. T0	-0.98%	3.67%	0.34160	0.16520
T30 vs. T0	-3.97%	5.88%	**0.02217**	0.11414

Statistical analysis performed: Student's paired t-test, $p < 0.05$ considered statistically significant.

By Day 14 **(T14)**, the average Rz value for B group was decreased by 0.98% as compared to its placebo counter part (A) increased by 3.67%; for "C", decreased by 3.48% compared with 2.85% increase in "A". Although the decrease in Rz showed a general trend toward anti-wrinkle efficacy by AdviCell shown as early as Day 14, these changes did not yet reach the statistical significance (p = 0.3416, 0.2405 respectively for "B" and "C"). By Day 30 **(T30)**, wrinkles were decreased most noticeably in Group C by 14.37% (p = 0.0006) Rz decrease (vs. 4.70% increase in "A").





Time	Mean Rz (mm)	
	C	A
T0	0.2340	0.1986
T14	0.2213	0.2032
T30	0.1913	0.2067

Time	% variations		p-value	
	C	A	C	A
T14 vs. T0	-3.48%	2.85%	0.24052	0.57302
T30 vs. T0	-14.37%	4.70%	**0.00060**	0.29421

Similarly, the B group shows 3.97% Rz decrease (p = 0.02217) compared with 5.88% increase in "A". In conclusion, both B and C groups demonstrated striking Rz value decreasing pattern (see black dotted arrows on the bar graphs), whereas the placebo A groups show either slight increase or no changes. AdviCell induced anti-wrinkle efficacy is shown to be dose-dependent: the higher AdviCell Content, 25%, in C formula significantly performed better than 10% content in A formula. This is a good scientific evidence that the AdviCell ingredient is directly responsible for wrinkle reduction.

III. SOLUTION: How Did AdviCell™ Improve the Prior Art?

H. AdviCell Improves Various Skin Conditions in Clinical Test Using It as a Sole Active Ingredient.

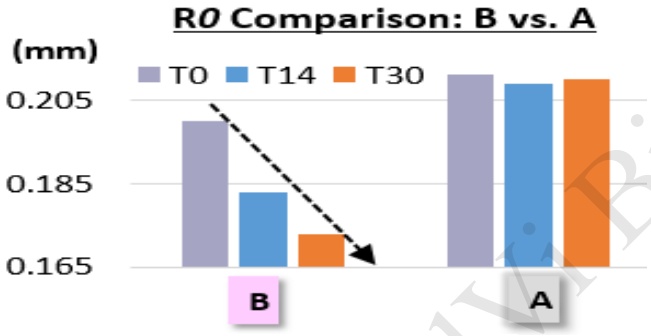
3) Increased Skin Firmness

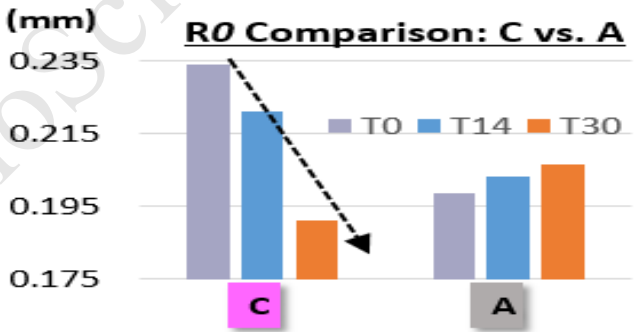
Skin Firmness (R*0*) represents the passive behavior of the skin to the application of the suction force which is related to skin firmness; **the lower is this value, the greater is skin firmness**. Multiprobe Adapter Systems MPA® (Courage-Kkazaka), equipped with Cutometer®, and Environmental Thermohygrometer (Courage-Khazaka GmbH - Germany) were used for this study. Refer to the manufacturer's website for detail description of how skin firmness is measured. www.courage-khazaka.de/index.php/en/products/scientific/128-mpa

Time	Mean R*0* (mm)	
	B	A
T0	0.200	0.211
T14	0.183	0.209
T30	0.173	0.210

Time	% variations		p-value	
	B	A	B	A
T14 vs. T0	-4.91%	-0.85%	0.1235	0.8701
T30 vs. T0	-8.33%	-0.58%	**0.0361**	0.9154

Statistical analysis performed: Student's paired t-test, $p < 0.05$ considered statistically significant.





Time	Mean R*0* (mm)	
	C	A
T0	0.227	0.207
T14	0.216	0.199
T30	0.231	0.184

Time	% variations		p-value	
	C	A	C	A
T14 vs. T0	-3.14%	-2.22%	0.3550	0.4931
T30 vs. T0	-9.51%	2.93%	**0.0046**	0.5639

By Day 14) **(T14)**, the average R*0* value for B group was decreased by 4.91% as compared to its placebo counter part "A" decreased by 0.85%; for "C", decreased by 3.14% compared with 2.22% decrease in "A". Although the decrease in R*0* showed a general trend toward improvement in skin firmness by AdviCell shown as early as Day 14, these changes did not yet reach the statistical significance ($p = 0.1235$, 0.3550 respectively for "B" and "C"). By Day 30 **(T30)**, skin firmness improved the most noticeably in Group C by 9.51% ($p = 0.0046$) R*0* decrease (vs. 2.93% increase in "A"). Similarly, the B group shows 8.33% R*0* decrease ($p = 0.0361$) compared with 0.58% decrease in "A". In conclusion, both B and C groups demonstrated R*0* value decreasing pattern (see black dotted arrows on the bar graphs), whereas the placebo A groups show either not much changed (for B's negative control) or even slight, gradual increase (statistically not significant though) for C's negative control counterpart.

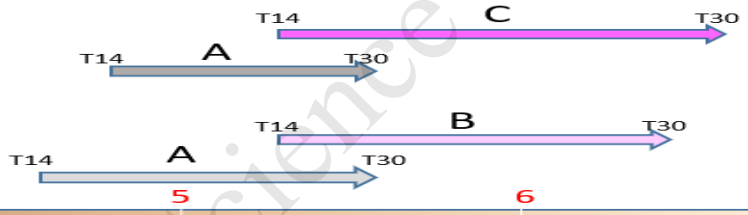
III. SOLUTION: How Did AdviCell™ Improve the Prior Art?

H. AdviCell Improves Various Skin Conditions in Clinical Test Using It as a Sole Active Ingredient.

4) Enhanced Skin Complexion

Minolta chromameter CR200 was used to measure an accurate and objective assessment of color surfaces: Data output is generated in the form of the L*, a* and b* color coordinate system pertaining to skin color. The three coordinates of CIE 1976 (L*, a*, b*) color space (also called CIELAB color space) represent the color lightness (L* = 0 yields black and L* =100 indicates diffuse white), its position between red/magenta and green (a*, negative values indicate green while positive values indicate magenta) and its position between yellow and blue (b*, negative values indicate blue and positive values indicate yellow). At each experimental time ΔE parameter (based on L*, a*, b* values) is calculated according to this formula: ΔE= √(ΔL*)2+(Δa*)2+(Δb*)2, in order to classify the difference in color. ΔE* values were calculated at the two time points, T14 and T30, to reflect the skin tone changes during T0-T14 and T14-T30 respectively. Interpretation of ΔE* parameters are annotated at the table inset below.

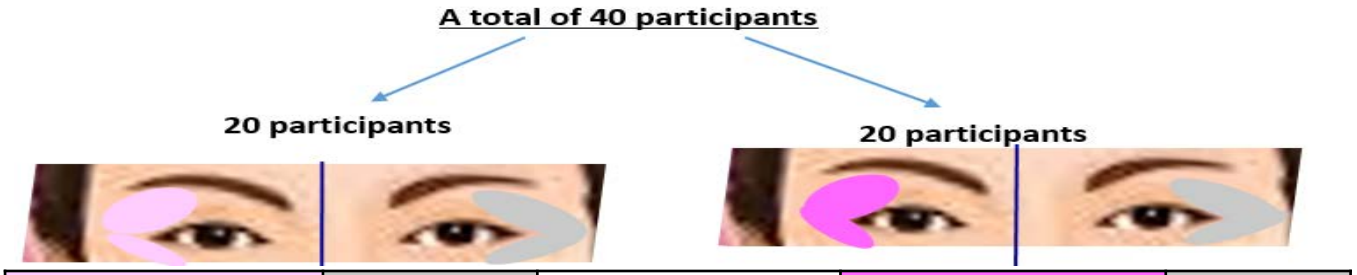
ΔE	Visual perception
2 ≤ ΔE ≤ 3	Visual
3 ≤ ΔE ≤ 6	Very Visual
6 ≤ ΔE ≤ 12	Strongly Visual



RESULT: "C" group containing the higher AdviCell concentration demonstrated the most robust progress toward the lighter complexion in terms of visually recognizable skin color, followed by "B" group of the lower AdviCell content. Both "A" groups of the corresponding placebo pool fell behind in complexion improvement.

Clinical study conclusion and representative Before/After photos obtained within the earliest measurement time point, i.e. 14 days: Throughout the three study categories (1. Anti-wrinkle, 2. Firmness, and 3. Complexion), apparent trends toward improvement started manifesting at day 14 time point in both "B" and "C" groups compared with the "A" placebo group. The positive effects were more noticeable from the higher AdviCell concentration group (C) than the lower (B). This dose-dependent response is an additional evidence that AdviCell is directly contributing to the skin rejuvenating effects. The above Before/After photos taken at Day 0 vs. 14 show **representative average improvement** among the participants. By Day 30, the dose-dependent regenerative trends held up to a statistically significant difference ($p<0.05$ by pair t-test).

Clinical Study (Day 30) Result Summary: average improvement when the placebo group is normalized to "no change".



10%	0%	AdviCell Content	25%	0%
Decrease by 9.85%	No Change	**Wrinkle**	Decrease by 19.07%	No Change
Increase by 7.75%	No Change	**Skin Firmness**	Increase by 12.44%	No Change
ΔE Value Increase by 0.06	No Change	**Skin Complexion**	ΔE Value Increase by 0.47	No Change

IV. CONCLUSION

Here we introduce a newly available conditioned media, CellVi's AdviCell, with considerable improvement over its existing counterparts in many performance characteristics. Most of the current conditioned media have various concerns, for example; 1) lack of complete list of the protein contents, 2) longer-term health safety, 3) perplexity in choice of cell type source, 4) lack of quality control & assurance measures, and 5) questions on its true contributory share to skin improvement. AdviCell significantly advanced the current art by a) identification of its entire array of protein/peptide contents and their associated cellular/molecular mechanisms, b) experimental evidences how it rejuvenates aged human skin cells in a growth regulatory manner, c) development of the QC/QA protein markers, and d) the considerable extent of clinical improvements manifested within 30 days' using AdviCell as a sole active ingredient. It is CellVi's future vision to continuously expand the comfort zone for the skin care industry and consumers for use of conditioned media. We are poised to accomplish this goal by persistent laboratory R&D efforts to successively create value added products.

V. REFERENCES:

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