

Knowledge Framework aiming at Disease Prevention through Logical Translation of the Balneology to the Modern Medicine

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温泉気候物理医学と現代医学の論理的橋渡しを通じた 疾病予防のための知識フレームワーク

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抄 錄

本論文では、疾病予防、健康維持を目指して、温泉気候物理医学において必要なトランスレーショナルリサーチおよびその知識処理フレームワークの基礎を明確化する。このために、ゲノムオントロジー、臨床オントロジー、温泉医学オントロジーをクライアントサイトにおいて橋渡しうる知識フレームワークとして、三つのコンセプトを提案する。第一は、論理的にミクロレベルからマクロレベルまでを統一的に拡張した解剖学的階層構造である。第二は、特徴記述された論理単位を基本とする知識記述方式であ

る。第三は、EBMに基づいた知識の質の評価である。本論文においては、知識フレームワークの基本構想と初步的な温泉医学知識を元にしたプロトタイプを構築した。論理的に拡張された解剖学的階層構造インデックスは、ゲノムから人/環境に至るまでの段階的階層構造に対してシームレスで論理的な連続性を提供することができた。EBMに基づいた知識の質の評価を加えることで、知識の信頼性が向上した。論理単位を基本とした知識記述方法により、粒度の異なる知識を单一の基準で扱うことができた。

Key words : *in silico, knowledge, translational research, balneology, disease prevention, health, life style disease, thermal aqua therapy*

I INTRODUCTION

The disease prevention and the health promotion is the essential targets worldwide from the view of the reduction of the medical care costs as indicated in the NIH (National Institute of Health) Road Map¹⁾ that shows the direction of NIH for the next decade from 2003. The hot spa therapy is a kind of the preventive medicine that can achieve the prevention through its systemic harmonization effect²⁾. The field of the hot spa therapy implies the temperature induced gene expression, the complex interaction between genome, phenotype, and environment. In this way, we can say that the hot spa therapy is a kind of the integrated environmental medicine and is a future target for the genomic research.

On the other hand, the translational research is the interdisciplinary practical experimental research aiming to bridge genomic science, clinical medicine, and other pioneer medicine³⁾. To proceed the translational research scientifically, we need to stand on the Evidence Based Medicine⁴⁾. Here considering that the evidence is the summation of the clinical cases and the good evidences should have the many clinical cases, the computerization of the knowledge and its migration is the inevitable consequence to support the translational research.

In this paper, we report the knowledge framework and its prototype that can apply to the translation among the genomic science, the modern medicine, and the hot spa therapy.

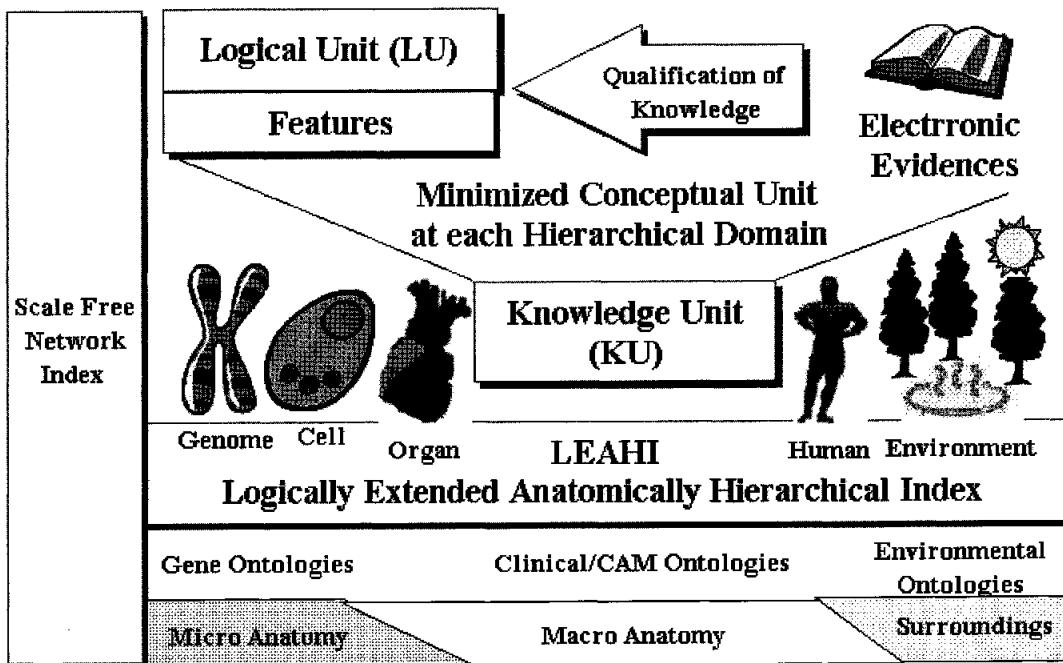


Fig.1 The Extended anatomical structure from micro to macro.

This structure has a Logically Extended Anatomically Hierarchical Index (LEAHI) as unified backbone. This index bridges genome, human, and environment logically. A knowledge unit is described as a set of a logical unit and electronic evidences. A logical unit is a minimized conceptual unit at each hierarchical domain and is described with its features. Each feature has its supportive evidence. Gene ontology, clinical ontology, CAM ontology, and environmental ontology are integrated with the single standard.

II METHODS

1. Knowledge Representation

In order to make knowledge bridgeable, we reconstructed the framework of the knowledge for the balneology and the western medicine to represent them with unified framework as the electronic knowledge on computers. For that purpose, we pigeonholed the knowledge based on the anatomical structure from micro to macro (Fig. 1). Because the knowledge about the environment is essential and fundamental in the field of the balneology, we set the environmental knowledge as superior hierarchy than biological species. This implies the integration of the Gene ontology, the Clinical/CAM ontology, and the Environmental ontology. Here the knowledge is represented with the Knowledge Unit that is the set of the logical conceptual unit and its Evidences. The logical conceptual unit is represented with its conceptual features. The conceptual features are normalized until the third level normalization within its residing hierarchy and its feature group. The evidences are stored their links to their knowledge unit as an evaluation basis of the knowledge qualification. The evaluation criteria are based on the Cochran collaboration designed EBM classification. We added the evaluation criteria for the books, the impact factor, and the citation index to evaluate the electronic media on Internet. The knowledge collection is achieved with embedding knowledge into the knowledge unit. Here the knowledge is extracted from the electronic media on Internet. The knowledge unit has the skeleton format that is designed by discovering the traits common to the stable knowledge. The clinical knowledge unit is described with the skeleton format (Fig. 2) for the disease knowledge and the anatomically hierarchical index. The genetic information as SNP is described with the balneologic information in a disease description.

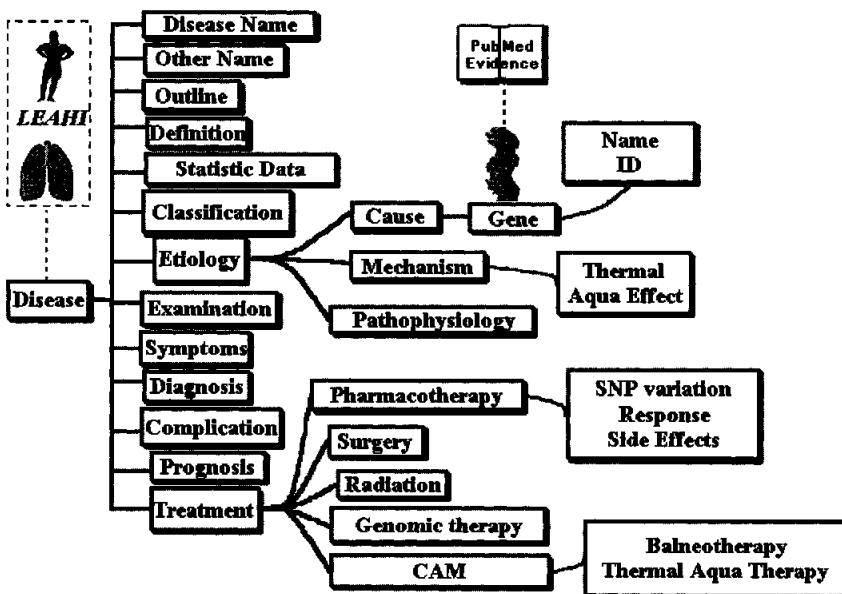


Fig.2 The clinical knowledge skeleton format.

The clinical knowledge skeleton format is based on disease classification as other international projects. The disease skeleton has features like disease name, other name, etc. Each knowledge unit of disease is composed to LEAHI and has links to evidence for each feature. The thermal aqua therapy and balneo therapy are combined with the genetic information as the SNP variation, side effects, and gene IDs.

2. The single architecture

The knowledge is sorted-out and stored with the single architecture. This single architecture is based on the unified summarizing concept that is the anatomically hierarchical structure from micro to macro. Here the human is the one of the biological species. Considering that the living organisms always have the interaction with the environment, we added the knowledge for the environment and positioned the environmental knowledge superior to the living organism. The knowledge for the hot spa itself and the natural environment is described within this environmental layer. We defined a knowledge unit as a set of the features and their evidences. The features are the diversified attributes of a concept. Each knowledge unit is indexed from the anatomically hierarchical index.

The evidences are the references to the electronic literatures that exist on WEB sites. The features are normalized to the third level normalization within a group that has the same feature at the same hierarchy, in order to minimize the redundancy and to optimize the size of the knowledge.

The disease knowledge units are formatted with the skeleton structure that is shared between the modern medicine and the hot spa therapy. Here the knowledge for the hot spa therapies are put into the knowledge of CAM (Complimentary and Alternative Medicine) in the treatment described in the disease.

The knowledge about the molecular network is summarized with the entity and the relation (Fig. 3). The entity and the relation are described with its features. The entity has the feature of the "Location" in the "Type".

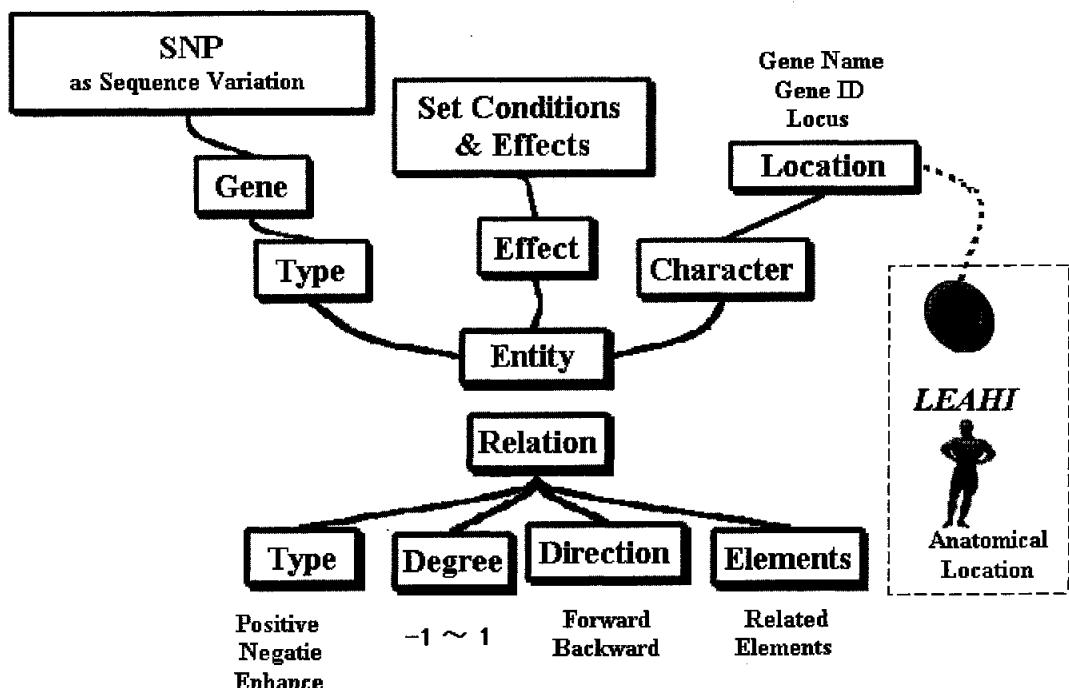


Fig.3 The skeleton format for the molecular biology.

The molecular biological findings are represented with entity and relation. The entity skeleton has the features of type, effect, and its character. An example of SNP data is described. The relation skeleton has the features of type, degree, direction, and elements. Examples are listed below each feature.

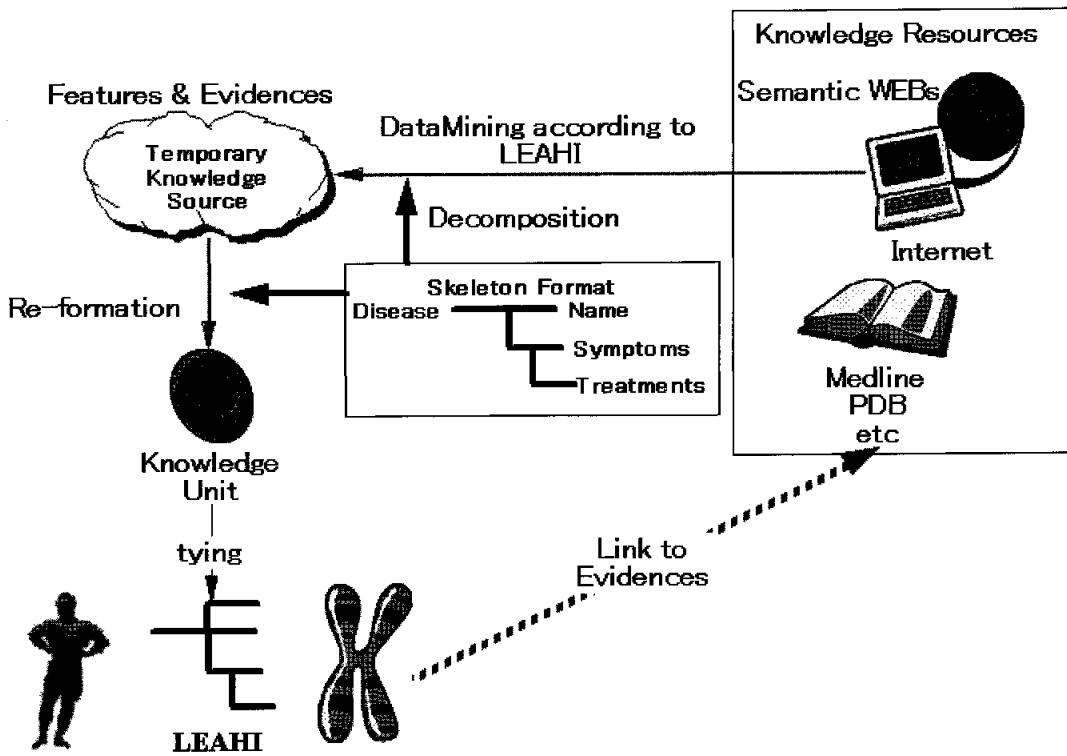


Fig.4 The outline of the knowledge collection.

The knowledge collection is achieved with the mining technology in the Semantic WEB world. The knowledge is decomposed to the parts, then recomposed to the knowledge units. In this recombination, the skeleton format is used to form the knowledge.

This “Location” feature is indexed from the anatomically hierarchical index. As an example, the “Location” of gene is described with the locus, ID, and its name. Generally, this “Location” is the place of the generation or the production. This is described in the database annotations. The “Effect” is described with its activating conditions. The relation is described with the features as the “Type”, the “Degree”, the “Direction”, and the “Elements”. Based on the theory of the Feinman Physics elementary process⁵⁾, these features are selected and defined. Through introducing this knowledge unit, the knowledge for the hot spa therapy can be related with the knowledge for the molecular biological knowledge.

3. Knowledge Collection

Fig. 4 shows the outline of the knowledge collection. The knowledge collection is achieved with locating the KU to the LEAHI. According to the LEAHI, we can collect the information from the Internet with data mining technology. The gathered information is diversified to the features and is composed to the knowledge unit as the logical unit and its evidences. The knowledge units are tied-on the LEAHI. The knowledge resources are the public database (Books, PubMed, PDBJ, PIR, Swiss Prot, PCB, Japana Centra Revuo Medicina Database, etc). We use some data mining tools (Cell Space, Pathway Assist)⁶⁾ in part as trial.

The knowledge collection is achieved with putting the knowledge units with according to the preset knowledge skeleton format and the preset knowledge index. The preset knowledge skeleton format is the proformas structure that is minimized its structural redundancy by the normalization. This is based on the extended anatomical structure. The anatomical structure is the easy-to-understand structure for both the biologists and the clinical researchers. Thus, this structure is less possibility to suffer the changes in its structure in the future. This means that this structure is sustainable.

The structure of the knowledge skeleton is based on the determinate and stable knowledge written in common with the plural books. The knowledge contents that are extracted from the publications are reformed to the knowledge unit by applying this knowledge skeleton.

Sporadically the knowledge that is extracted from the publications includes the concepts that have not reached a stable consensus in the medical society. This means that the extracted knowledge has the possibility to change and the instability. In such case, the quality evaluation of the knowledge is significant.

The knowledge resources are the published electronic media, the reviews, and the committee reports from the Public DB (PubMed, PDB, PIR, Swissprot, PCB, Medicina DB)⁷⁾. The collection of the knowledge was performed with the data mining tools (Pathway Assist, Cell Space)⁸⁾. They are based on the knowledge categories that are predefined in the client ontological classification table. The knowledge collection in the Semantic Networks on Internet is achieved with locating the extracted KU collections to the LEAHI. Here the knowledge is collected with the general data mining technology according to the theme derived from the LEAHI. The theme is the concrete entity or the relation that are described in the LEAHI. The figure shows the ideal automation process. We use some data mining tools to collect the parts of the knowledge manually in the prototype. Each gathered information is diversified into the features according to the skeleton format and the diversified features are stored as the knowledge parts source with its supportive evidences or the reasons in the temporary database. The stored features are used to compose the logical unit. Each feature of the logical unit has the links to its evidences or the reasons. This means that the knowledge unit is formed as a set of the logical unit and its supportive evidences. According to the LEAHI, we arrange and locate the collected knowledge from the Semantic WEBs on Internet with the data mining technology. The knowledge units are tied to the LEAHI according to the preset collection theme. The knowledge resources in the Semantic WEB on Internet are the public databases or the ontologies such as the electronic books, the PubMed, the MEDLINE plus, the GenBank, the PDB, the PIR, the Swiss Prot, the SCOP, the Japana Centra Revuo Medicina Database, and etc.

4. Evidences

The evidences are evaluated their qualities with the quality evaluation table (Table 1). This table is based on the EBM Cochran classification table. We added the criteria for the books and the classification with the impact factor or the citation index in order to establish the seamless qualification and the quantitative evaluation. Considering that the criteria of the quality evaluation is not stable itself in the time course, the storing evidences are limited to the links of the documents. Thus, the evaluation was performed with this table for the same reason.

III PROTO TYPE AND RESULTS

The prototyped knowledge for the hot spa therapy was built. The knowledge for the hot spa therapy is extracted from the balneologic books. The knowledge of the hot spa therapy is decomposed to the parts and is rebuilt-in

Table 1 Quality classification table of evidences

Quality	Major class	Sub-major class	Minor class	Sub-minor class
High	Book Paper	Many-sided Universality	Number of supports	Impact Factor and Citation Index
		Randomized Controlled Trial (RCT)	Multiple support	
			Meta-analysis over multiple RCT's (conclusions may differ)	
		Non-Randomized Controlled Trial (non-RCT)	Single RCT conclusion	
		Quasi-experimental studies	Comparative studies, correlation studies etc.	
	Case series, case report, etc	Cohort studies, case-controlled studies, etc	Number of supports	
Low	WEB site	Opinions from experienced experts	Comments of committee, etc	

This table is based on EBM cochrane collaboration design, and we add books and sub-minor class to evaluate electrical media. In this table, highest quality evidence has many sided universality in many books.

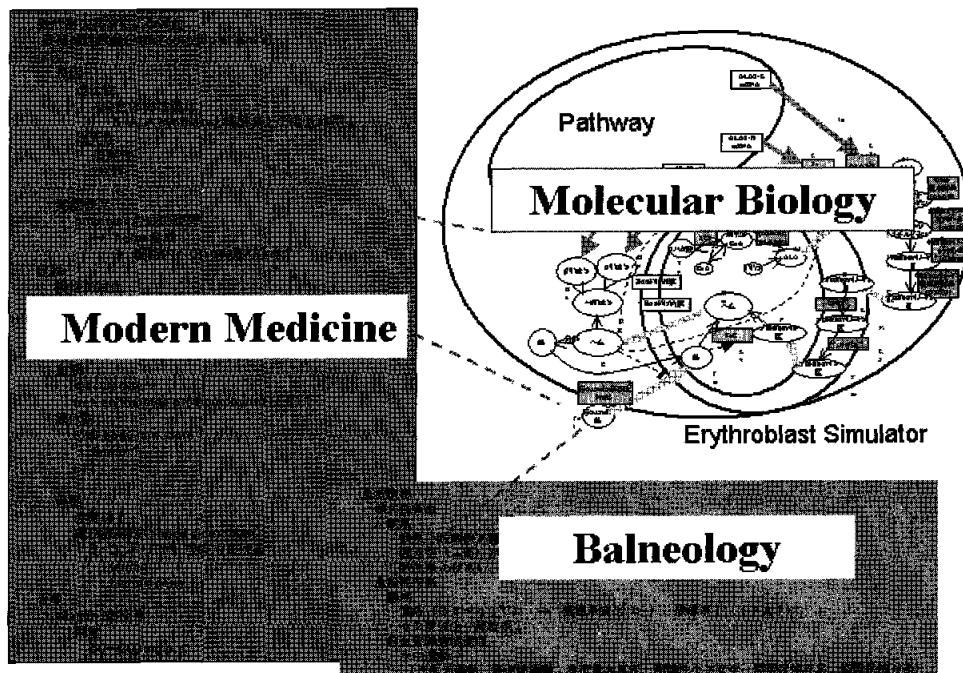


Fig.5 The ideal relation of the modern medicine, the balneology, and the genomic science in Japanese. Through theme of sideroblastic anemia, multi disciplinary knowledge are integrated. These knowledge are bridged with single backbone LEAH.

to the integrated knowledge that has the index of the modern medical enhanced anatomy. The integrated knowledge was built by indexing the anatomically hierarchical index to the knowledge parts that are extracted from the hot spa therapeutic publications. The knowledge concerning about the genomic science is collected with using the data mining tools. Additionally we developed the prototype software to achieve the easy operability.

Fig. 5 shows the relations among the hot spa therapy, genomic science, and the modern medicine in the prototyped knowledge. The contents of the knowledge are described in Japanese. This knowledge is bridged with the anatomically hierarchical structure that is the unified frame.

A part of the screen of the prototype is shown in Fig. 6. This example is for the Iron Deficiency Anemia (IDA) coupled with the erythrocytic differentiation schema. The anemia is a kind of the red blood cell disease, and the IDA is a kind of the anemia. In this example, the IDA is defined in the hierarchy of the cytoplasm. The anatomical path is shown in the left of the Window. Clicking the IDA in the cytoplasm pops up the explanation of the IDA in the center of the Window. The features of the IDA are shown as the outline processor. Double clicking the mechanism of the sideration widen and pops up its explanation. Clicking the term of the balneotherapy pops up its explanation. Thus if need, clicking the acid spa pops up its explanation. The evidences for the clicked entities are shown in right below Window. The color of the evidence is the same as the clicked term. The erythrocytic differentiation is aligned with their functions.

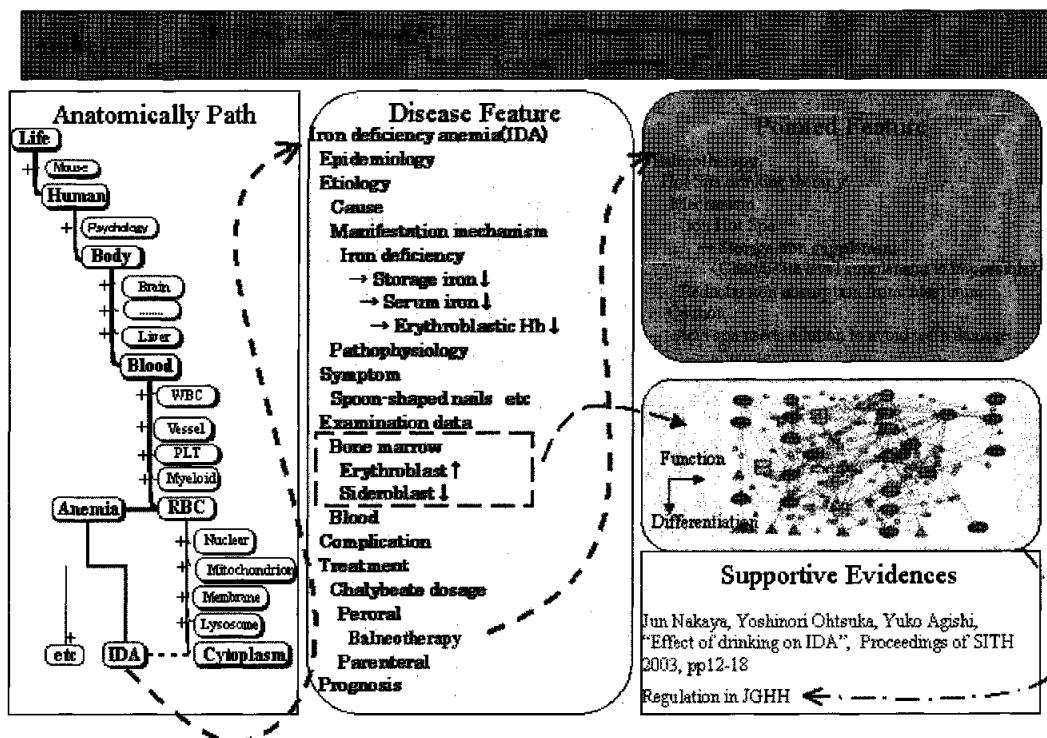


Fig.6 A sample window concerning about the IDA coupling with the erythroblast simulator. This figure shows the relation between the modern medicine, the bioinformatic simulator, and the balneotherapy. With clicking the starting button, the erythroblast simulator starts.

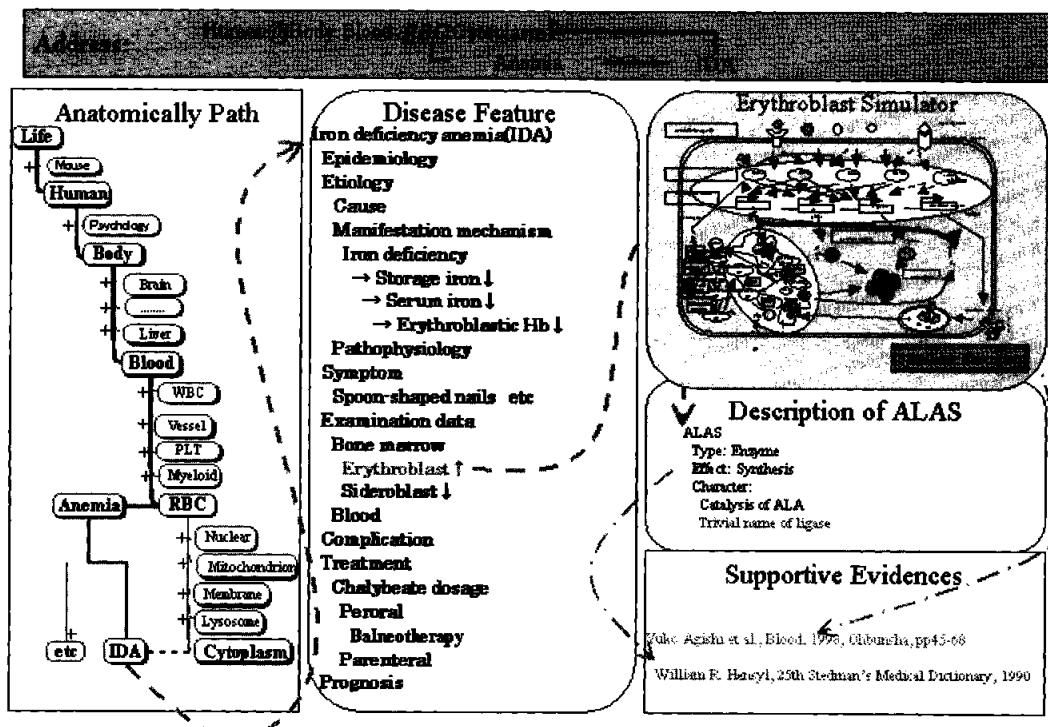


Fig.7 A sample window for the Iron deficiency anemia (IDA) coupled with the differentiation-function coordination. The modern medical knowledge, the balneological knowledge are coupled as the single knowledge.

Fig. 7 is an example of the screen that shows the molecular biological findings of the IDA knowledge. This example has the erythroblast simulator in the upper right Window. Clicking the ALAS (δ -AminoLevulinic Acid Synthetase) in the erythroblast simulator pops up the explanation of the ALAS that is along to the skeleton format. Clicking the simulator button starts the erythroblast simulator. This skeleton has the terms of the type, the effect, and the character. The lower right window shows the evidences for the character of the trivial name.

IV DISCUSSION

The future image of the balneotherapy is shown in Fig. 8. The clinical objectives are to enhance the Quality Of Life (QOL), the clinical efficiency, and the clinical safety. Ultimately it means the disease prevention. To establish the disease prevention, we need to predict the future clinical events and to avoid the critical clinical situations. Only the knowledge can be the background for the future events prediction. The fundamental approach of the disease prevention is to establish the sure-footed knowledgebase.

To establish the precise prediction by analyzing the multi-dimensional input information, we need plenty of the precise knowledge. To predict the clinical situation, the knowledge quality and its evaluation method are important issues as the basis of the prediction.

In the medical domain field, EBM exists as the methodology to evaluate the quality of the knowledge. EBM is

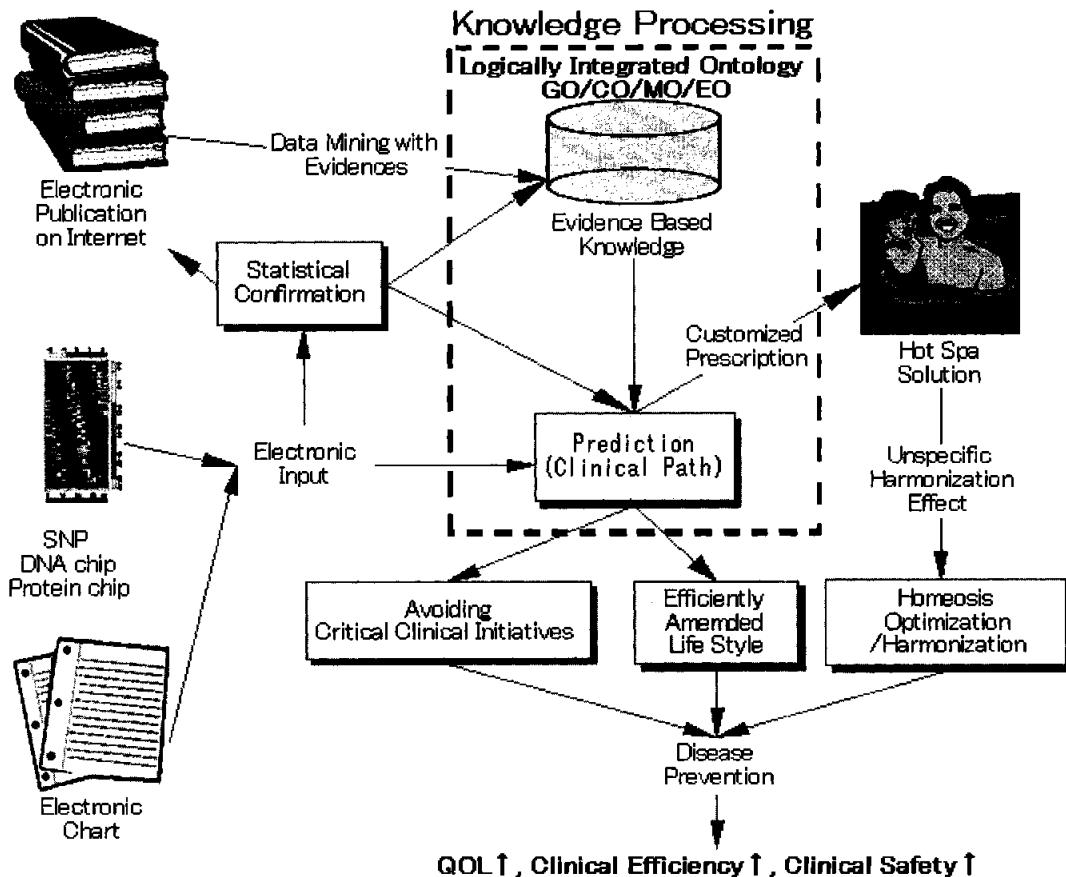


Fig.8 The future Image of the Balneotherapy

The balneotherapy is combined with the genome-based diagnosis and the prediction. The modern medicine, the genome technology, and the balneotherapy are effectively integrated.

getting to be the international standard in the medical field, in the current medical context, the knowledge should be sorted out with the EBM concept.

To provide the on-target balneotherapy, not mass production but the customized, personalized, and optimized hot spa therapy is essential. The integrated genomic technologies like Micro-Array or Protein chip are important for the personalized medicine as a scientific data input. Considering that the improvement of the prediction needs the variety of the input data, the integrated genomic technologies can be the scientific input data to increase the information. The evaluation and the certification of the data by the biological statistics are important for both the knowledge formation and the judgment of the input data. In the near future, the patient chart must be computerized to use it as one of the electronic input. These future therapies will be established when the logical integration of the multi-disciplinary knowledge is established.

Basically, the translational research is the multidisciplinary practical research aiming to bridge the basic medical science, the clinical medicine, and the other fields bi-directionally through the knowledge integration. This

translational research is the bridging research to introduce the novel methodology of the diagnoses or the therapies. Historically the translational research is popular among the cancer research, the application for the genomic field starts recently. We try to apply the informational technology that is developed for the smooth translational research in the balneotherapeutic field. We began the bridging research between the balneotherapy and the modern medicine. This time we designed the basic structure of the integrated knowledge that is the nucleus of the translational research and the knowledge itself.

The conceptual integration between the balneology and the traditional medicine is possible through describing the knowledge as the *in silico* electronic knowledge with unified architecture. This unified architecture makes the bi-directional migration of knowledge between them smoothly. This smooth migration expands the options of therapy, the Quality Of Life (QOL), and enforces the strategic medical research.

Adding the evidences as the components of the KU leads to concretize the basis and the quality of the description by the evidences. This addition can groom the overflowed information of the balneologic field that includes a mixture of good and bad. This evidence based grooming makes the EBM effective in the clinical scene.

Amid calls for the EBM as the background of the scientific diagnosis and therapy, this evidence based grooming can be an answer how we can establish the EBM in balneology. In the EBM, the quality of the evidence is important. As for the classification method of the evidences, the cochrane collaboration design gives a criterion. Considering that the balneologic fields have stored the many findings at many countries before American medicine got to be standard, the reuse or the salvage of those valuable findings through the text mining can lead to find the scientific novelties and backgrounds. As for applying EBM to the balneology, Prof K. L. Resch indicates the needs⁹.

This research aims to bridge the modern medicine, the balneology, and the genomic research. In the current context, the bridging between the modern medicine and the genomic research has already begun and is in progress. Here the essence of the bridging is the knowledge. Treating the knowledge *in silico* enables the smooth migration of knowledge between the basic medicine and the clinical medicine. This directly leads to the strategic medical research.

The current translational research based on the *in silico* technology starts its urgent progress from 1995 in the context of the rapid progress of the IT evolution. At NIH, the translational research is defined as the knowledge migration research between the basic medicine and the clinical medicine. They emphasize the importance of the electronic knowledge that can bridge the fields. Corresponding to this movement, the project "GALEN" tries to bridge the clinical medicine and the molecular medicine through the disease based indexing¹⁰. These computerizations of the knowledge and its use are the international breaking research in biomedical field. In Japan, the Clinical Genomics Center at the Kobe University starts the research.

As for applying the electronic knowledge to the medical fields, the ontological project named "PROTEGE" is under way. This is the ontological tool with its application projects by the Stanford Medical Informatics (SMI)¹¹. Based on this tool, SMI developed the "EON" system that is for the protocol based care¹². Recently the gene ontology (GO) project that try to summarize the ontological dictionary for the genome domain knowledge is under way¹³. However, the developing of the intellectual translational research system using the ontological dictionary has not started yet.

Data mining and text mining are the technology to collect the electronic knowledge on Internet. Adriane Genomics Inc. and Cellomics Inc. released some product tools for this purpose. We used these tools to collect knowledge in part. Expert system, fuzzy inference, and neural network are the method to achieve the prediction with the electronic knowledge. The molecular modeling, the pathway model, GON¹⁴⁾, and the virtual reality are the method to achieve the prediction from the points of the molecular modeling. The biostatistics based clinical informatics is the way to analyze the clinical data¹⁵⁾. The digitalization process of the image processing is one of the methods to digitalize the features of the knowledge¹⁶⁾.

In this paper, we extracted the balneologic knowledge from not only the electronic media but also the publications. However, considering that the electronic media is essential to introduce the automated process, the establishment of the international electronic database is immediately required.

In advance to the drug based modern therapy, the balneotherapy does not have the chemical side effects. The pre-treatment stage like the disease prevention or the health promotion is apparently different from the cure stage at the point that the target persons are not patient but healthy people yet have potential to be a patient. Considering the preposition that the side effects as the treatment risk is not affordable for the healthy people, the disease prevention and the health promotion based on the balneotherapy will be one of the solutions to fulfill the requirement of the modern health promotion approach. Integrating the genome findings that has the meaning of the modern scientific reasoning and the balneotherapy that has the meaning of the internal harmonizer for the health promotion as the system medical science make the genome findings effective in the clinical field. Moreover, we can establish the new stage of the medical field that can avoid diseases.

V CONCLUSION

1. We could show the successful example that the logically extended anatomically hierarchical index and its knowledge structure can be the single and sharable architecture to assemble the modern clinical medicine, the hot spa therapy, and the genomic medicine.
2. Storing the features of a concept and their links to the evidences as a combined set enables the evaluation of the quality of the knowledge component and the knowledge itself. This leads to work EBM effectively in the hot spa therapy.
3. The methodology of the genomic translational research informatics can give the scientific backgrounds to the balneology. These scientific backgrounds give the equivalent scientific basis to the modern medicine.
4. The single architecture that has the anatomically hierarchical index and the feature described concepts could achieve the seamless continuity of the knowledge structure among the modern medicine, the genomic medicine, and the balneology. This means that the architecture can be the logical basis for the smooth translation.

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Summary

The objective of this paper is to define the basis for the translational research and its knowledge framework in balneology aiming to approach the disease prevention. As a method to attain this objective, we advocate the knowledge framework that can bridge gene ontology (GO), balneologic ontology (BO), and clinical ontology (CO) virtually at a client site with three sided basic concepts as (1) the logically extended anatomical index from micro to macro, (2) the knowledge representation based on feature described logical conceptual unit, and (3) the EBM (Evidence Based Medicine) based quality evaluation of knowledge. As an result, the scheme and the prototype of the knowledge framework for the basic balneology was built. The logically extended anatomically hierarchical index could offer the seamless and logical continuity from genome to human/environment. The EBM based quality assessment enhanced the reliability of knowledge, and the knowledge representation based on the logical conceptual unit approach offered the unification of the different grain size knowledge.