


약 력

1. 인적사항

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2. 학력/경력

연 도	학교 / 기관	전공 / 직위	학위 / 비고
1988	서울의대 졸	의학	
1995	서울의대 석사	뇌영상술	
1998	서울의대 박사	뇌영상술	
1997	하버드의대 연구전임의	의료정보학	
2000	MIT 석사	의료정보학	
2000	하버드의대 전임강사	Biomedical Informatics	
2001	하버의의대 조교수	Biomedical Informatics	
2001	서울의대 교수	Biomedical Informatics	

3. 주요연구실적(개조식, 간단하게)

4. 발표시 사용 기자재

- * LCD projector의 사용을 원칙으로 합니다.
- * LCD 사용을 위해 CD나, 저장 매체에 담아 오시는 것을 권장하며, Zip드라이브는 학회에서 준비하지 않습니다.

TMA-OM(Tissue Microarray Object Model)과 주요 유전체 정보 통합

서울대 의대 부교수 김 주 한

Tissue microarray (TMA) is an array-based technology allowing the examination of hundreds of tissue samples on a single slide. To handle, exchange, and disseminate TMA data, we need standard representations of the methods used, of the data generated, and of the clinical and histopathological information related to TMA data analysis. This study aims to create a comprehensive data model with flexibility that supports diverse experimental designs and with expressivity and extensibility that enables an adequate and comprehensive description of new clinical and histopathological data elements.

We designed a Tissue Microarray Object Model (TMA-OM). Both the Array Information and the Experimental Procedure models are created by referring to Microarray Gene Expression Object Model, Minimum Information Specification For *In Situ* Hybridization and Immunohistochemistry Experiments (MISFISHIE), and the TMA Data Exchange Specifications (TMA DES). The Clinical and Histopathological Information model is created by using CAP Cancer Protocols and National Cancer Institute Common Data Elements (NCI CDEs). MGED Ontology, UMLS and the terms extracted from CAP Cancer Protocols and NCI CDEs are used to create a controlled vocabulary for unambiguous annotation.

We implemented a web-based application for TMA-OM, supporting data export in XML format conforming to the TMA DES or the DTD derived from TMA-OM. TMA-OM provides a comprehensive data model for storage, analysis and exchange of TMA data and facilitates model-level integration of other biological models.

Availability: Xperanto-TMA is available at <http://xperanto.snubi.org/TMA/>.

Keywords: tissue microarray, data model, data exchange, XML, object model, DNA microarray

TMA-OM (Tissue Microarray Object Model)과 주요 유전체 정보 통합

Ju Han Kim, M.D., Ph.D.

<http://www.snubi.org/>

최종 연구 개발 목표

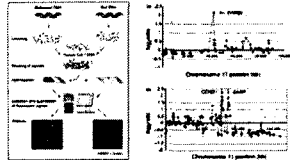
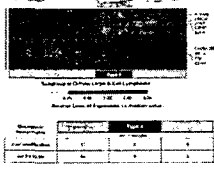
DNA microarray, Tissue microarray, array CGH와
암유전체 임상정보 통합 데이터베이스 및 분석시스템 개발

- 3대 유전체 분석 기술의 통합 모델링 및 통합 데이터베이스 구축
 - DNA microarray
 - Tissue microarray
 - array CGH
- 암 유전체 연구의 조직병리 및 임상정보 통합 모델 개발
 - CAP Cancer Protocol
 - NCI CDE
 - HL-7 CDA
- 정보공유를 위한 XML 메시징, 파싱 및 입출력 인터페이스 기술 개발
- 통합 분석 시스템 구축



연구의 배경 및 필요성

Rosenwald et al., 2002 NEJM
High throughput 바이오정보로
악성종양의 치료결과 예측 및 치료방침 결정의
자료로 사용할 수 있음을 제시



array CGH 분석을 이용한
유전체 구조 분석을 통한 유전체
이상 정보의 식별
Transcription Response 200 BAC probe 158 9.2

당면 해결과제:

기술통합 (다양한 DNA칩, BAC칩, TMA칩)과
정보통합 (임상정보, 유전체정보, 분석기술)의
확보가 실제 임상적용의 핵심 과제

3대 유전체 정보 획득 기술

1 DNA microarray

- 단일 조직
- transcriptomal regulation
- gene expression
- 유전자 발현 검출 병렬화

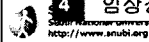
2 arrayCGH

- 단일 조직
- genomic structure
- copy number alteration
- 유전체 변형 검출 병렬화

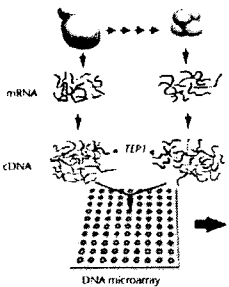
3 Tissue microarray

- 단일 유전자 / 단백질
- tissue anatomy level
- gene/protein expression
- 인구집단 병렬화 (population)

4 임상정보 암 임상정보 통합



DNA microarray



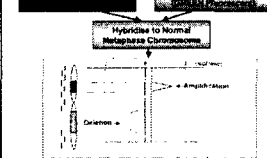
단일 조직
수만 개의 유전자
유전자 발현
유전자 검출을 병렬화

arrayCGH

- 현재까지 알려진 유전체 상환물에서 가장 빈번히 발견되는
유전자 변형은 염색체의 미세한 변형 (중복, 결손, 전위)임
- Karyotyping, FISH, SKY 등으로는 충분한 정보를 얻을 수 없음
- CGH의 기술적 한계를 마이크로배리어와 BAC 클론으로 해결함

단일 조직
수천개의 BAC 클론
유전자 변형
유전체 변형 분석 병렬화

Comparative Genomic Hybridization (CGH)



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Tissue microarray

a

조직 표본에서
원기종 모양의
Core 획득
(직경 0.6mm)

b

Recipient Block에
Core 이식
(수백회 반복)

c

관측성 광물으로
조직 마이크로어레이
제작 > 1,000 장
(두께 0.1mm)

Morphology

RNA content

복수 조직
조직정보 포함
단일 검출 (다양한)
병리조직을 병렬화

Target	Probe	방법
단백질	항체	면역조직화학법
DNA	DNA, fluorescent labeled	FISH
RNA	RNA, biotin labeled	in situ hybridization
Virus	primers	in situ PCR
DNA	primers	methylation specific in situ PCR

Tissue microarray

4.0 mm	2.0 mm	1.0 mm	0.6 mm
24 specimens	60 specimens	140 specimens	240 specimens
SuperBioChips			

3대 유전체 정보 대량 획득 기술

Genome structure, BAC Clone, Gene, Gene function, DNA microarray, Transcriptional regulation, Gene expression, MAGE, array CGH, Genomic Structure, Copy number alteration, Clinical Information, Histo-pathological Information, Tissue microarray, Tissue anatomy level, Gene / Protein / RNA / DNA / Virus, High throughput Validation, Population-based analysis, (Linking genomic & clinical info.)

조직병리 정보 (X)
조직 공여자의 임상정보 (X)
현 슬라이드에 여러 개체의 조직

어레이 데이터 모델링/표준화 한계의 극복

MGED (Microarray Gene Expression Data) Group

MIAME: what to store (data specification)
MAGE-OM: how to store (object model)
MAGE-ML: how to communicate (XML representation)

cannot integrate

- arrayCGH : partly be represented → extend/adjust MAGE-OM
- TMA : not at all → develop TMA-OM(CDE and ontology)
- Histopathology: none → CAP Cancer Protocol, CTEP
- Clinical information: none → NCI CDE, HL-7 CDA
- Data exchange → XML-based middleware
- Data management → Web-based database
- Data analysis modules → Web-based analysis modules
- High-level combined analysis result → develop integrated system

Introduction Tissue Microarray

- Tissue microarray (TMA)
 - An array-based technology (Kononen *et al.*, 1998)
 - Analysis of molecular alterations in hundreds of tissues on a single slide in parallel
 - Used for identifying molecular marker in cancer research
 - High-throughput validation tool of marker genes from a DNA microarray analysis

Integration of DNA microarray and high-density TMA is emerging as powerful approach to molecular profiling of human cancer.

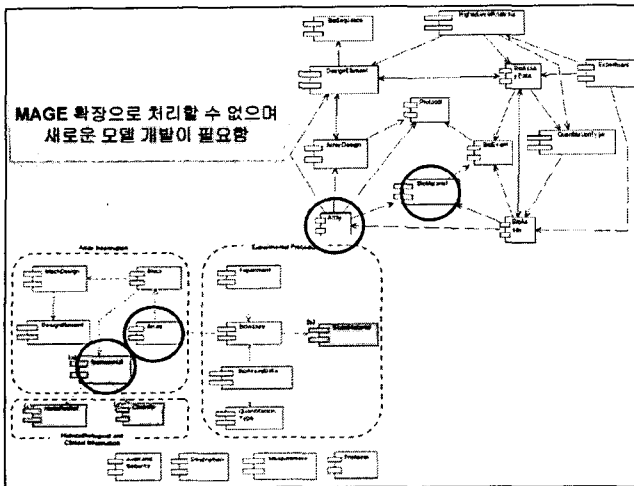
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Introduction Tissue Microarray

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Motivation Related Work

	DNA Microarray Data	Proteomics Data	TMA Data
Minimum Information Specification	MIAME	MAIPE	TMA Data Exchange Specification
Data Model	MAGE-OM	PSI-OM	Not available
XML format for Data Exchange	MAGE-ML	PSI-ML	TMA Data Exchange Specification
Implementation	ArrayExpress and so on.	PEDRo	Manley et al.(2001) and so on.

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Motivation Characteristics for TMA data model

- The data model needs
 - Expressivity in whole information concerning TMA
 - Flexibility in the design of TMA experiments
 - Controlled vocabulary and standards for data exchange
 - Extensibility to additional clinical and histopathological data on cancers
- Why not MAGE-OM?
 - TMA is different from DNA microarrays in the aspect of materials on array features.
 - Annotation of a TMA feature contains properties of each tissue sample including clinical and histopathological information.

→ Data model for TMA data, like MAGE-OM for DNA microarray data, is needed

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Table 1. Comparison of related works and this study

Data model	Generalized clinical and histopathology information model	Numbers of cancers supported	Extensibility for other cancers	Integration with MAGE-OM	Controlled Vocabulary	
Manley et al., 2001	ER Model	Not included	1 (prostate cancer)	No	Not easy	Not considered
Shklovskich et al., 2003	ER Model	Not included	1 (large cell lymphoma)	No	Not easy	Not considered
Demichellis et al., 2004	ER Model	Not included	2 (breast and lung cancer)	No	Not easy	Not considered
Berman et al., 2004	XML Database	Not included	1 (prostate cancer)	No	Not easy	CPTC CDEs and TMA CDEs
Nperantzis-TMA	Object Model	Model based on CAP Cancer protocols and NCI CDE	Forty three cancers	Yes	Easy	MGED Ontology, UMLS and terms extracted from CAP Cancer Protocols and NCI CDEs

ER Model: Entity Relationship model, CAP: College of American Pathologists, NCI CDE: National Cancer Institute Common Data Element, MAGE-OM: Microarray Gene Expression - Object Model, CPTC: Cooperative Prostate Cancer Issue Reviews, MAGE: Microarray Gene Expression Data

Method Object Model

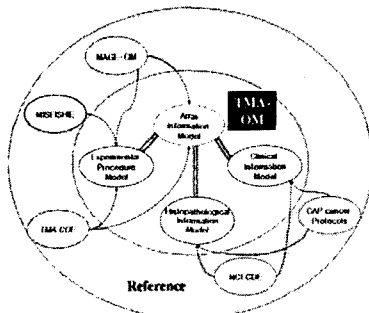


Figure: Architecture of Tissue Microarray Object Model (TMA-OM).

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Material For Array Information and Experimental Procedure Models

- Microarray Gene Expression - Object Model (**MAGE-OM**)
 - Standards to represent microarray gene expression data
 - Applicable to a broader set of array style experiments
 - Standardization of annotation - controlled vocabulary in MGED ontology
- Minimum Information Specification For In Situ Hybridization and Immunohistochemistry Experiments (**MISFISHIE**)
 - a Data Standard of IHC and *in situ* Data
 - developed in a MISFISHIE Working Group within the MGED Society
- TMA Common Data Elements (**TMA CDEs**)
 - XML tag used for TMA Data Exchange Specification (Berman et al., 2003)

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All packages in MAGE-OM

Material For Clinical and Histopathological Information Model

- NCI Common Data Element (NCI CDE)
 - To promote a common nomenclature and vocabulary across various organizations performing cancer research.
- College of American Pathologists (CAP) Cancer Protocols
 - Standardization of surgical pathology report
 - 46 Cancer Protocols are available in 2006 revision

MACROSCOPIC

Specimen Type
 ___ Excision
 ___ Metastasis
 ___ Other (specify) _____
 ___ Not specified

Lymph Node Sampling
 ___ No lymph node sampling
 ___ Sentinel lymph node(s) only
 ___ Sentinel lymph node with auxiliary dissection
 ___ Auxiliary dissection

Specimen Size (for excisions less than total metastomy)
 ___ Unavailable
 ___ cm
 ___ Cannot be determined (see Comment)

Lateality
 ___ Right
 ___ Left
 ___ Not specified

Tumor Site (check all that apply)
 ___ Upper outer quadrant
 ___ Lower outer quadrant
 ___ Upper inner quadrant
 ___ Lower inner quadrant
 ___ Central
 ___ Not specified

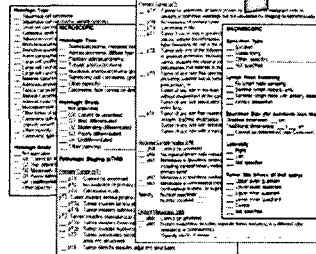
Example: Breast Cancer Protocol - Checklist

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Method Object Modeling: An Example

Example: Histopathological Information Modeling

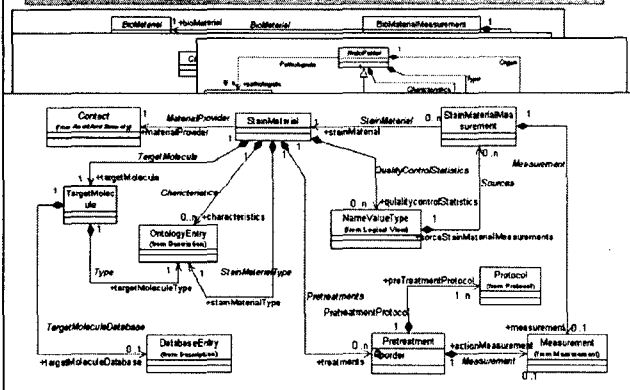
•43 Cancer Protocols



- BasicHistoPathol
 - Tumor Info
 - PrimaryTumor
 - RegionallyLymphNode
 - DistantMetastasis
 - TumorSite
 - TumorSize
 - Histology
 - Histologic Type
 - Histologic Grade
- OrganSpecific

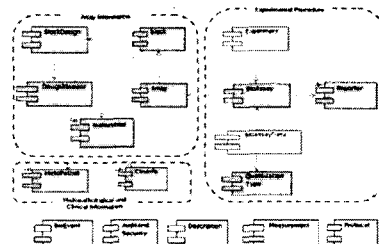
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Method UML-based Development of Object Model



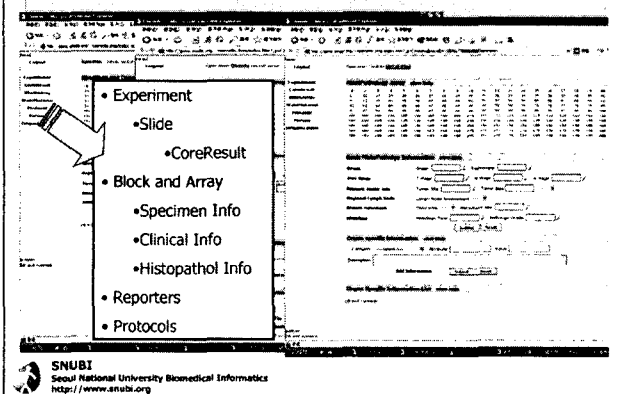
Result Tissue MicroArray Object Model (TMA-OM)

- TMA-OM is a data model to represent tissue microarray data and related information such as clinical and histopathological information.
- 17 packages, 111 classes
 - Array Information Mode
 - Experimental Procedure
 - Clinical and Histopathol
- Implementation
 - Web-based relational database



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Implementation Xperanto-TMA: Block and Array submission



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Xperanto-TMA Usage of Controlled Vocabulary

Controlled Vocabulary

Basic Histopathology Information

Value	Description	Action
PT0	Cannot be expressed	SELECT
PT1	No evidence of primary tumor	SELECT
PT2	Tumor 2.0 cm or less in greatest dimension	SELECT
PT3	Tumor more than 2.1 cm but not more than 3.5 cm in greatest dimension	SELECT
PT4	Tumor more than 3.6 cm but not more than 5.0 cm in greatest dimension	SELECT
PT5	Tumor more than 5.1 cm but not more than 7.5 cm in greatest dimension	SELECT
PT6	Tumor more than 7.6 cm but not more than 10.0 cm in greatest dimension	SELECT
PT7	Tumor more than 10.1 cm in greatest dimension	SELECT
PT8	Tumor of any size with direct extension to chest wall or skin	SELECT
PT9	Tumor of any size with direct extension to chest wall or skin, extension to chest wall, not including ipsilateral muscle	SELECT
PT10	Tumor of any size with direct extension to chest wall or skin, extension to chest wall, not including ipsilateral muscle, extension to chest wall or skin	SELECT

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Implementation Xperanto-TMA: Data Export

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Discussion Integration with other biological data model

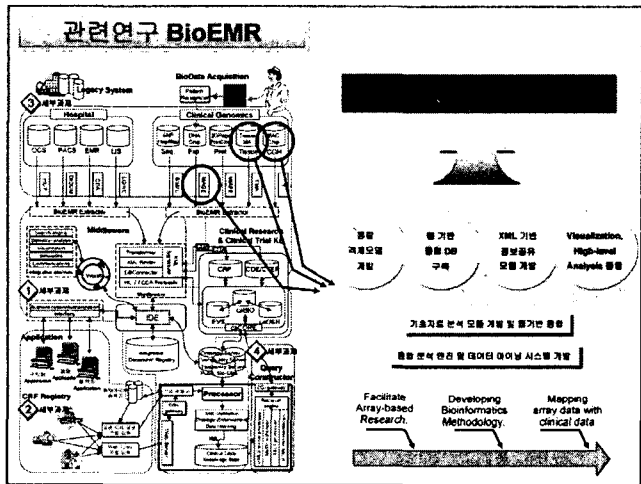
- Integration with **DNA microarray** and **arrayCGH** data using MAGE-OM
 - *Reporter* classes in TMA-OM and MAGE-OM equally represent reporters to identify a specific molecule such as a gene
 - *Specimen* class in TMA-OM corresponds to the *BioSource* class in MAGE-OM
- with **proteomics** and **metabolomics** data using
 - PEDRo or PSI-OM which are object model for proteomics data
 - Functional Genomics Experiment Object Model (FGE-OM, Jones et al., 2004) or data model for Systems Biology (SysBio-OM, Xirasagar et al., 2004) which are data model extended from MAGE-OM

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Conclusion

- TMA-OM allows
 - Represent TMA data with standardized term
 - Add clinical information and pathological information on new tissue
 - Add expression profile and annotation of target molecule (protein and gene) with TMA data
- TMA-OM is helpful to integrate with other data model such as MAGE-OM (gene expression profile) and PEDRo (proteomics data).
- TMA-OM provides a comprehensive data model for storage, analysis and exchange of TMA data and facilitates model-level integration and analysis of other biological models like MAGE-OM.

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Thank you!

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