

Outline

- Observed Convergence Paths
- Nano-Fluidics Convergence Example
- Molecular Imaging Convergence Example
- Clinically Driven Convergence Example

```
nWindowState = START_WINDOW;
DisableDIRQ();
nRevCounter--;
nLEDTurn = 0;

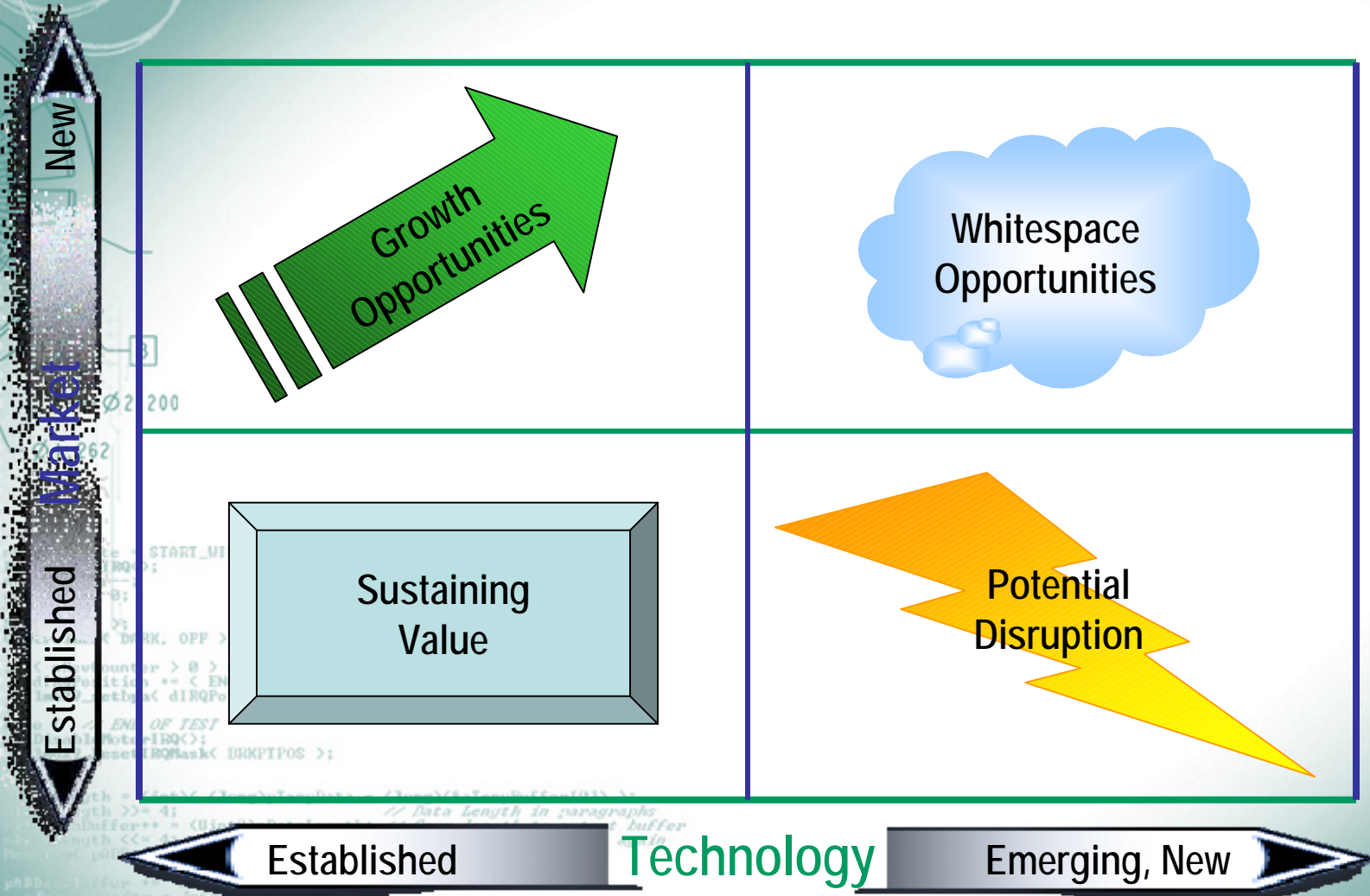
SetGain( 1 );
ControlLED( DARK, OFF );

if ( nRevCounter > 0 ) {
  dirQPosition += ( ENCODER_RES - nWindowEnd + nWindowStart );
  In629_setDirQ( dirQPosition );
}
else { // END OF TEST
  DisableMotorIRQ();
  In629_ResetIRQMask( BRKPTPOS );
}

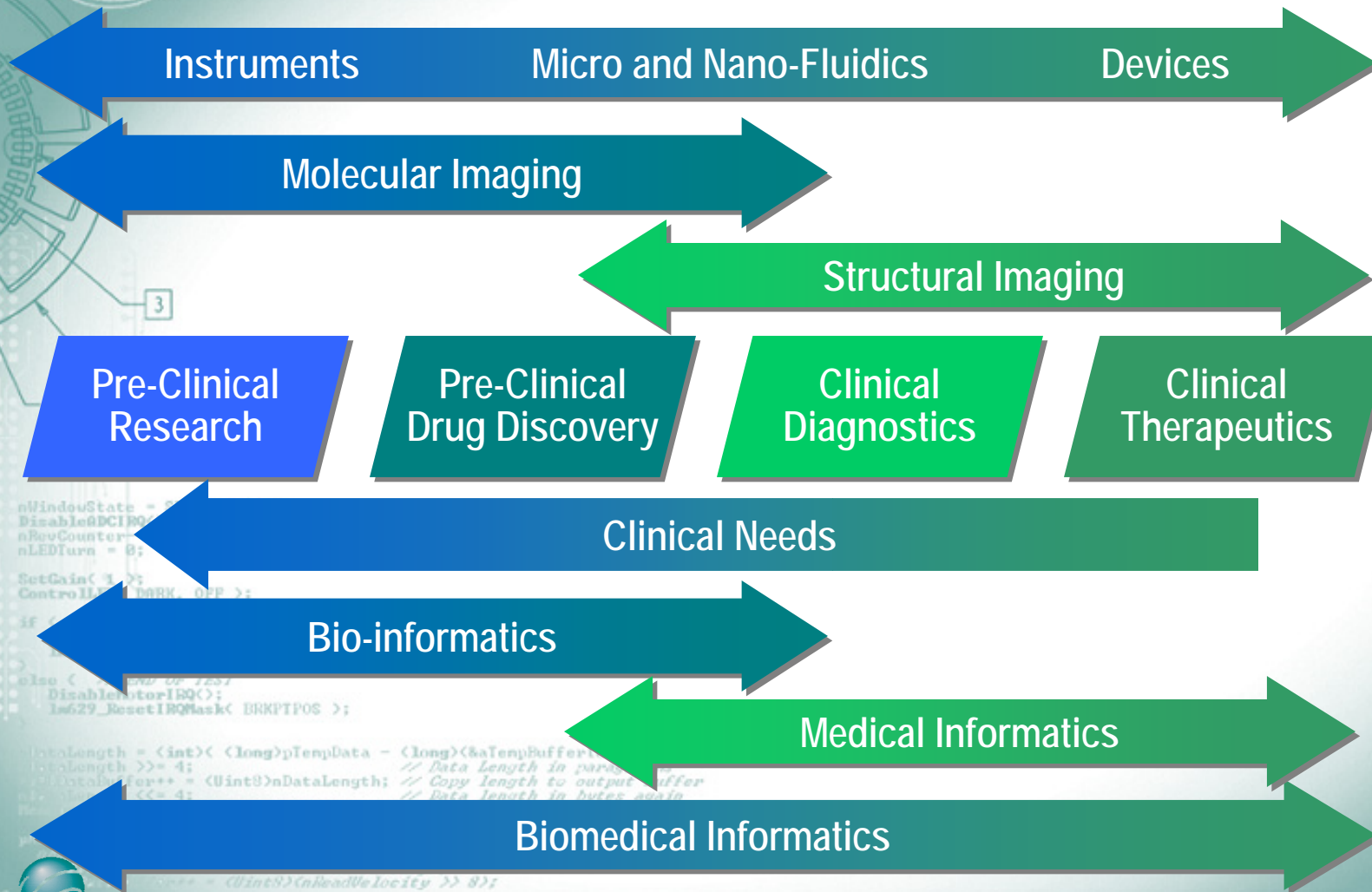
nDataLength = (int)( (long)pTempData - (long)&aTempBuffer[0] );
nDataLength >>= 4; // Data length in paragraphs
pDataBuffer += (uint8)nDataLength; // Copy length to output buffer
nDataLength <<= 4; // Data length in bytes again
memcpy( pDataBuffer, aTempBuffer, nDataLength );

pDataBuffer += nDataLength;
nHeadVelocity = In629_readVel();
nHeadVelocity += (uint8)(nHeadVelocity);
nHeadVelocity += (uint8)(nHeadVelocity >> 8);
```

Strategic Innovation Opportunity Space



Parallel Technology Paths that Support Biotechnology Innovation



Nano-Fluidics Convergence Example



Pre-Clinical Research

Pre-Clinical Drug Discovery

Clinical Diagnostics

Clinical Therapeutics



Innovation Source: Bioinstrumentation Laboratory at MIT

- Multi-disciplinary laboratory headed by Prof. Ian Hunter
- All researchers must be fluent in at least two disciplines:
 - Biology, Chemistry, or Biotechnology AND
 - Mechanics, Electronics, Optics, Mathematics, or Information Technology
- Groundbreaking work in nanotechnology applications for biotechnology and drug delivery



Innovation Results: BioTrove – OpenArray and LivingChip

- **Massively Parallel Nano-Array Systems**
 - Over 25,000 Array elements per Slide
 - Compatible with Conventional Micro-plate Readers
- **Convergence of Mechanical/Fluidics with Biotech Applications**
 - Elegant Simplicity of Architecture
 - Utilizes Basic Material Properties paired with Basic Fluidics Properties
- **Convergence of Informatics with Molecular Libraries**
 - Libraries of Bio-informatics Data
 - Libraries of Molecules in Chips

```
nWindowState = START_WINDOW;
DisableBDCIRQ();
nRevCounter--;
nLEDTurn = 0;

SetGain( 1 );
ControlLED( 0 );

if ( nRevCounter > 0 ) {
  dirQPosition += ( ENCODER_RES - nWindowEnd + nWindowStart );
  In629_sethqa( dirQPosition );
}
else { // END OF TEST
  DisableMotorIRQ();
  In629_ResetIRQMask( BRKPTPOS );
}

nDataLength = (int)( (long)pTempData - (long>(&nTempBuffer[0]) );
nDataLength >>= 4; // Data length in paragraphs
nDataBuffer++ = (UInt8)nDataLength; // Copy length to output buffer
nDataLength <<= 4; // Data length in bytes again
memcpy( pOutDataBuffer, aTempBuffer, nDataLength );

pOutDataBuffer += nDataLength;
nDataLength = In629_readvel();
nDataBuffer++ = (UInt8)(nDataLength);
nDataLength <<= 4;
memcpy( pOutDataBuffer, aTempBuffer, nDataLength );

// for new velocity
for ( i = 0; i < nDataLength; i++ )
  pOutDataBuffer[i] = nDataLength;
```



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Innovation Results: BioTrove – Massively Parallel Antibody Phase Screening

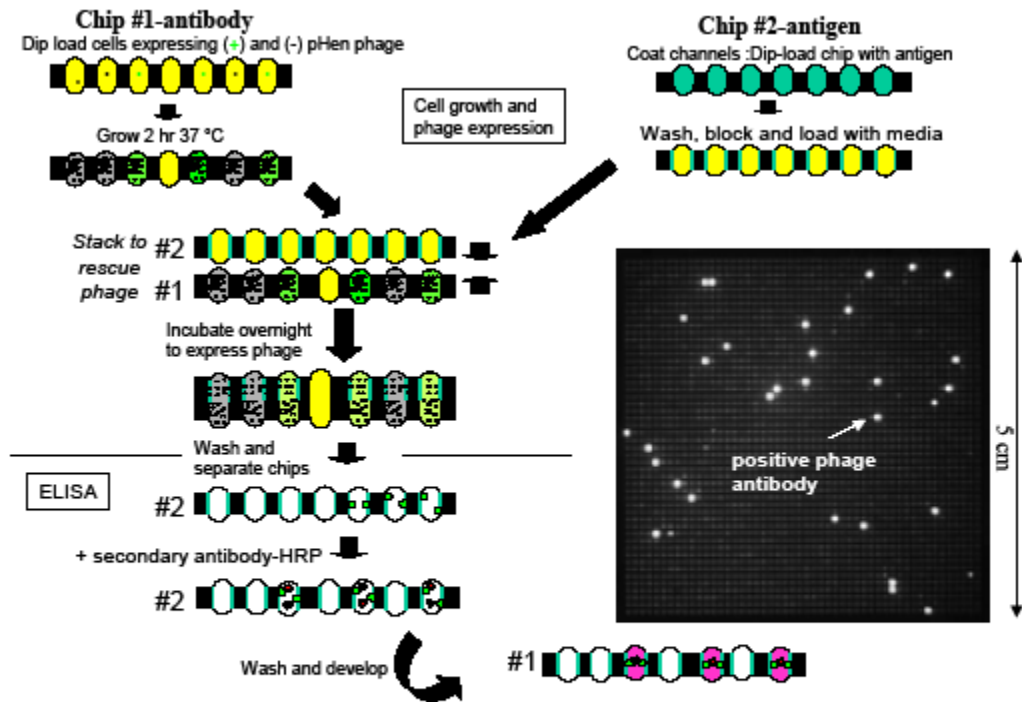


Figure 7: Outline of protocol for antibody phage library screening including the ELISA assay steps. An antibody library was dip-loaded into one 10,000-channel chip, cultured for two hours and then stacked with a 10,000-channel antigen chip. The stacked arrays were incubated, washed and separated and the antigen chip developed with a standard ELISA protocol to generate fluorescent signal in channels where there was a high affinity antibody-antigen complex.

```

nWindowState = START_UI
DisableDCIRQ();
nRevCounter--;
nLEDTurn = 0;

SetGain( 1 );
ControlLED( DARK, OFF );

if ( nRevCounter > 0 ) {
  dirQPosition += ( EN
  1s629_setha( dirQPo

} else ( // END OF TEST
  DisableMotorISRQ();
  1s629_ResetISRQMask(

}

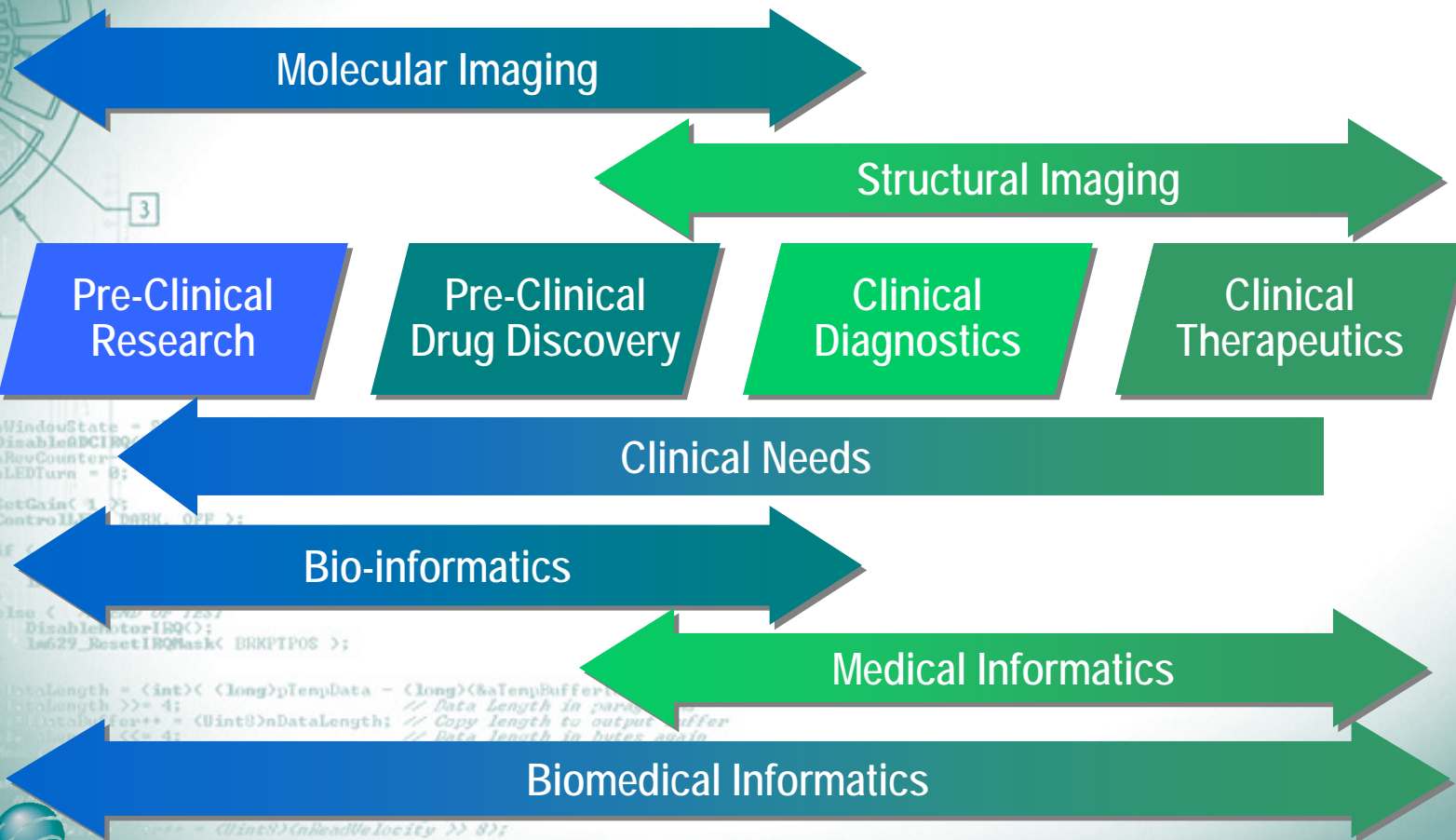
nDataLength = (int)( (1
nDataLength >>= 4;
nDataBuffer++ = (Uin
nDataLength <<= 4;
nDataBuffer++;

pDDDataBuffer ++ nDataLength;
nDataBuffer = InS27_readoe1();
nDataBuffer++ = (UinS)(nReadVelocity);
nDataBuffer++ = (UinS)(nReadVelocity >> 8);
  
```

Innovation Commercialization

- BioTrove has successfully closed over \$20 million in financing
- Major pharmaceutical partners for Drug Discovery
 - Pfizer
 - Others (undisclosed)
- Commercially available OpenArray Systems
 - SNP Genotyping
 - qPCR Transcript Analysis
 - Pathogen Detection
 - ELISA Testing
- Broad Intellectual Property Portfolio
 - Core Patents licensed from MIT
 - Conflicting Patents acquired from Genecor
 - Application Patents licensed from Stanford

Molecular Imaging Convergence Example



Innovation Source: Center for Molecular Imaging

Massachusetts General Hospital, Harvard Medical School

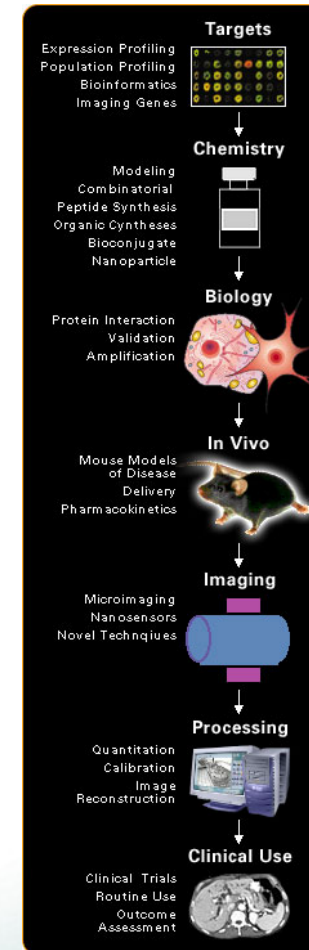
- Multi-disciplinary laboratory headed by Dr. Ralph Weissleder, MD, PhD

- Cross-disciplinary team covering:

- Molecular Biology
- Cell Biology
- Biochemistry
- Bio-informatics
- Radiology
- Cardiology
- Oncology
- Immunology

- World-leading research in the molecular phenomena of disease.

- Ultimate target, *in vivo* sensing and imaging of molecular level events.



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Innovation Results: MGH/VisEn/SIEMENS – Fluorescent Molecular Tomography

- *In Vivo* 3D imaging of Biochemically Active Sites
 - Mouse Animal Model
 - Oncology and Atherosclerosis Targets
 - Pharmacological Activity Verification
- Convergence of Biochemistry with Optical Engineering and Image Processing with Biotech Applications
 - Exceptional specificity
 - Tomographic Image Reconstruction
- Convergence of Structural Imaging with Molecular Diagnostics and Imaging
 - *Ex Vivo* Diagnostic Screening
 - *In Vivo* Diagnostic Imaging
 - *In Vivo* Guided Therapy



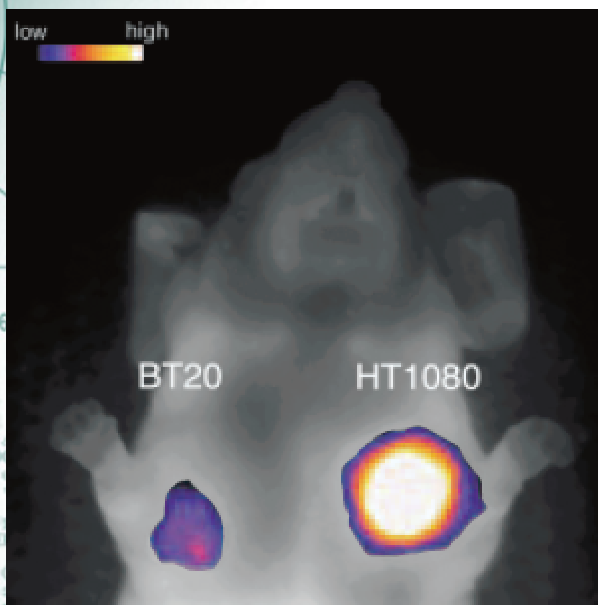
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Innovation Results: MGH/VisEn/SIEMENS – *In-Vivo* Imaging



7] COLOR-ENCODED near-infrared fluorescence image of a mouse, implanted with two different human breast tumors, differing in tissue invasiveness. The mouse was injected with a fluorochromes-labeled smart probe, activated by cathepsin-B. The agent is more activated in the more invasive right tumor. (Image courtesy of Ralph Weissleder, CMIR).

Endoscopic NIRF Imaging for Detection of Colon Cancer (Murine Model)

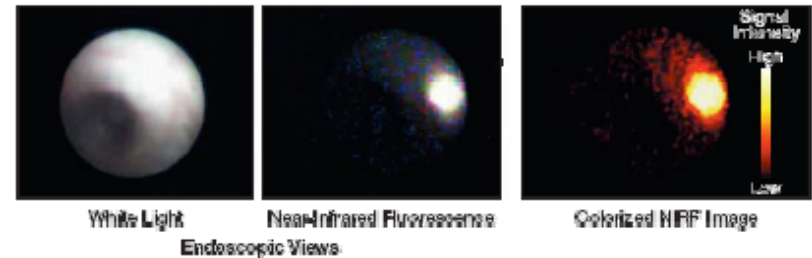


Table 2. Optical/NIRF and Ultrasound Molecular Imaging Agents*

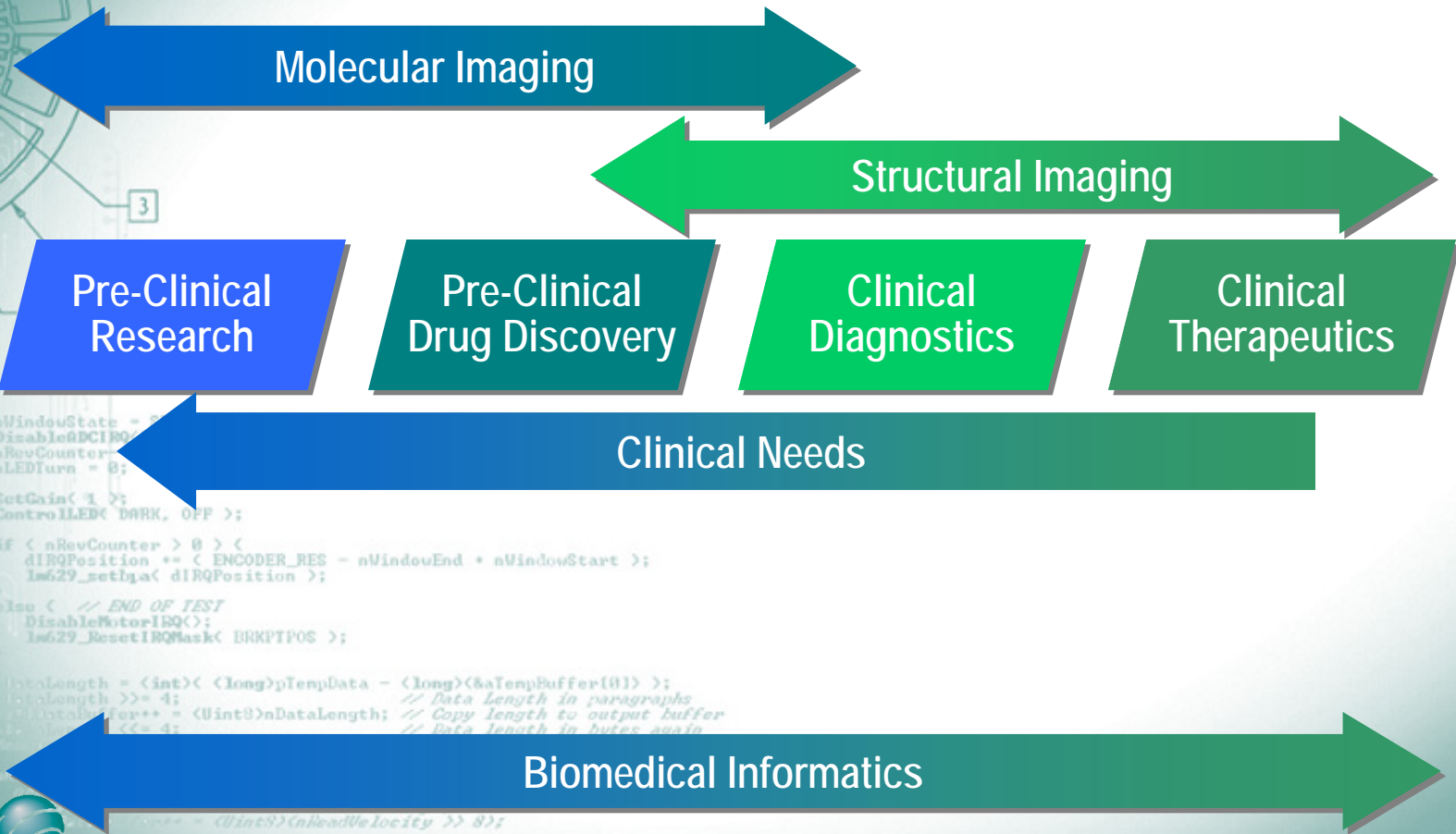
Disease	Imaging Technology	Imaging Agent	Clinical Application
Cancer	Optical/NIRF	Cathepsin B	Many cancers
		Matrix metalloproteinases	Many cancers
		Targeted fluorochromes (her2neu, annexin A5, etc)	Many cancers
Atherosclerosis (vulnerable plaque)	Ultrasound	Integrin $\alpha\beta_3$	Angiogenesis
	Optical/NIRF	Cathepsin B	Inflammation
		Matrix metalloproteinases	Inflammation
		Annexin A5	Apoptosis
		Fibronectin	Angiogenesis
	Ultrasound	Vascular cell adhesion molecule 1	Inflammation
Vascular cell adhesion molecule 1		Inflammation	
Thrombosis	Optical/NIRF	Plasmin	Acute thrombi
		Factor XIIIa	Acute thrombi
	Ultrasound	Fibrin and fibrinogen	Acute/subacute thrombi
Neurological	Optical/NIRF	Tissue factor	Acute thrombi
		Activated integrin $\alpha\beta_3$	Platelets
		Pittsburgh compound B	Alzheimer dementia
Arthritis	Optical/NIRF	Cathepsin B	Inflammation
		Diphosphonate	Osteoclast activity

Abbreviation: NIRF, near-infrared fluorescence.
*Animal experiments only to date, with clinical trials anticipated. Imaging agents were compiled from a literature search in PubMed. The list is meant to be representative and not exhaustive. For more in-depth information on recent advances, please consult references 4, 7, 17, and 35. Imaging agents that do not exhibit cellular uptake/binding are excluded.

Innovation Commercialization

- VisEn has received major equity investments from Siemens
- Major pharmaceutical partners for Drug Discovery
 - Novartis
 - Others (undisclosed)
- Commercially available bonSAI Imaging System through Siemens for Pre-Clinical Research and Drug Discovery
- “The adaptation of fluorescent optical techniques to diagnostic imaging is now changing the way we visualize molecular processes in vivo, and ultimately, in the clinic.”
Dr. Ralph Weissleder, MD, PhD, Director CMIR

Convergence Around a Clinical Need Example



```
nWindowState = 0;
DisableDCIRQ();
nRevCounter = 0;
nLEDTurn = 0;

SetGain( 1 );
ControlLED( DARK, OFF );

if ( nRevCounter > 0 ) {
  dirQPosition += ( ENCODER_RES - nWindowEnd + nWindowStart );
  I629_setba( dirQPosition );
}
else { // END OF TEST
  DisableMotorIRQ();
  I629_ResetIRQMask( BRKPTPOS );
}

DataLength = (int)( (long)pTempData - (long)&TempBuffer[0] );
DataLength >>= 4; // Data length in paragraphs
OutputBuffer++ = (UInt8)nDataLength; // Copy length to output buffer
DataLength <<= 4; // Data length in bytes again

// ... = (UInt8)nLeadVelocity >> 8);
for new velocity
  *pOutData+BufferIndex = ...
  break;
default:
  break;
```

Innovation Source:

Center for Integration of Medicine and Innovative Technology
MGH, BWH, Harvard Medical, MIT, Draper Labs

- Multi-disciplinary organization tapping talent at Major Research Hospitals, Medical and Technology Research Centers
- Example Program: Vulnerable Plaque “Living Laboratory”
- Unique multi-organization cooperative environment, guided by clinical needs and *clinical realities*



```
nWindowState =  
DisableDCIRQ(  
nRevCounter--;  
nLEDTurn = 0;  
SetGain( 1 );  
ControlLED( DN  
  
if ( nRevCount  
dIRQPosition  
Is629_seth  
  
else ( // END  
DisableMotorISQ(  
Is629_ResetIRQMask( BRKPTPOS );  
  
nDataLength = (int)( (long)yTempData - (long)&aTempBuffer[0] );  
nDataLength >>= 4; // Data length in paragraphs  
pOutDataBuffer++ = (UInt8)nDataLength; // Copy length to output buffer  
nDataLength <<= 4; // Data length in bytes again  
memcpy( pOutDataBuffer, aTempBuffer, nDataLength );  
  
pOutDataBuffer += nDataLength;  
nDataLength = Is629_readoe1(  
nDataLength / 4; // (UInt8)nReadVelocity;  
nDataLength / 4; // (UInt8)nReadVelocity >> 8);  
  
<C> 7/14/1998  
for new velocity  
pOutDataBuffer++ =  
break;  
default:  
break;
```



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Innovation Results: Emerging *In Vitro* Diagnostics, *In Vivo* Imaging and Therapy

- More than 20 Collaborative Programs Underway
- Major Pharma, MedTech and Startup Participation
 - J&J Cordis
 - Medtronic
 - Guidant
 - Boston Scientific
 - GE Amersham
 - Terumo
 - InfraReDx
 - Epix Pharmaceuticals
 - Pharmacyclics
 - Miravant
 - Thermacore/BMS
 - Light Sciences
- Convergence of Screening, Imaging and Therapeutic Options
 - In-vitro Screening
 - Non- and Minimally-Invasive Intra-vascular Imaging
 - Therapeutic Agents (some with Intra-vascular Activation)

Innovation Commercialization

- Initial Pre-Clinical Commercialization of Diagnostics and Therapies
 - => Heavily Guided by Clinical Community
- Strong Cooperation Among Major Pharma and MedTech Players
- Major Clinical Trials coordinating Diagnostics and Therapeutics

- Broad Intellectual Property Cross-Licensing

- Low Risk Screening drives need for Interventional Diagnosis
- Interventional Diagnosis drive Therapies
- Many Therapies rely on intra-vascular technologies
- Availability of Therapies drive use of Screening



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