The Emergence of Flow Cytometry as a Routine Diagnostic Testing Technology – Right Here in Our Own Back Yard!

Mike Reed
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Danaher designs, manufactures, and markets innovative products and services to professional, medical, industrial, and commercial customers.

Driven by strong core values and a foundation provided by the Danaher Business System, Danaher's associates are pursuing a focused strategy aimed at creating a premier global enterprise.

- Founded 1984
- Headquartered in Washington, DC
- New York Stock Exchange Listed (DHR)
- ~58,000 associates worldwide
20-Year Total Shareholder Return
DHR vs. S&P 500

Outperforming over the long term
4X revenue base and continuing to evolve the portfolio while outperforming the market
Multi-Industry with Strong Brands

Environmental
Test & Measurement
Dental
Life Sciences & Diagnostics
Industrial Technologies

- HACH
- FLUKE
- TEKTRONIX
- Kerr
- Beckman Coulter
- Videojet
- Lange
- Trojenuv
- Tektronix Communications
- Ormco
- Leica Microsystems
- ESKO
- ChemTreat, Inc.
- DEXIS
- AB SCIEX
- LNX
- Gilbarco Veeder-Root
- FLUKE Networks
- Pelton & Crane
- Radiometer
- Linx
- Molecular Devices
- Thomson
Life Sciences & Diagnostics Overview

~$34B
Market Size

5-7%
Long Term Market Growth

$4.6B
2011 Sales
65% Instruments | 35% Consumables / Service

8.7%
2011 Operating Margin

Geographic Mix
(as % of 2011 sales)
- 31% ROW
- 37% NA
- 32% EU

Brand | Market Position
---|---
Beckman Coulter | #1 / #2
Leica Microsystems | #2
AB SCIEX | #1
Radiometer | #1
Molecular Devices | #1 / #2

Customers
- Hospitals
- Reference labs
- Government/academic research
- Food & beverage, pharmaceuticals, forensics
Helping customers unlock tomorrow's discoveries
Beckman and Coulter: Two of the most respected names in the industry

- Arnold O. Beckman, Ph.D.: inventor of the acidimeter
- Wallace and Joseph Coulter: discovered the Coulter Principle
- Created a company dedicated to improving patient health and reducing the cost of care
  - More than 275,000 systems operate in laboratories on every continent

Our inspiration: Improving patient health and reducing the cost of care
Diagnostics Technology Leadership

- Chemistry
- Immunoassay
- Hematology
- Information Systems
- Clin Lab Automation
- Molecular Diagnostics

We enable physicians to make patient healthcare decisions
Life Sciences Technology Leadership

- Flow Cytometry
- Centrifugation
- Life Science Automation
- Capillary Electrophoresis
- Particle Characterization
- Genomics

We empower researchers with solutions to accelerate scientific breakthroughs
• Marseille
• Galway
• Danvers
• Miami
• Indianapolis
• Fort Collins
• Carlsbad
• Brea
Life Sciences

Flow Cytometry
What is Flow Cytometry?

Sample: Cells +/- Fluorescent labels

Flow Cell

Laser light source

Fluorescent light collected

Reflected and transmitted light collected
Beckman Coulter Flow Cytometry

Global Development & Manufacturing

#2 in the market

Primary Customers

Clinical diagnostics

Basic research and biomarker discovery

Clinical studies and trials

60%

25%

15%
Beckman Coulter Flow Cytometry
Marseille, France

Reagent development and manufacturing for Flow Cytometry
Hardware and reagent manufacturing and development for Flow Cytometry – Kendall, Hialeah, Pembroke Pines
Product design and development for Flow Cytometry Sorters
Our Portfolio

165 IVD/CE-IVD products
473 ASR products
1,900 RUO products

Multicolor Combinations
Custom Design Service
Contract Manufacturing Service
New Products Launched in 2012

165 IVD/CE-IVD products
473 ASR products
1,900 RUO products

Multicolor Combinations
Custom Design Service
Contract Manufacturing Service
Surface, Intracellular, and Functional Analysis

Providing complete solutions for specimen and data handling to study:

T cells, B cells, monocytes, macrophages, granulocytes, stem cells, cancer, microparticles, platelets

Surface Marker Analysis
(Constitutive and activation-dependent receptors)

Cell Function Analysis
(Pathway activation and inhibition)

Intracellular Marker Analysis
(Cytosolic and nuclear markers)
What is it used for?

Testing for HIV+ progression to AIDS – CD4 enumeration
Fully Automated load & go™

1. LIS System Receives Test Requests
2. Load Blood Specimens
3. Go Operator Walks Away... System Does the Rest
4. Results System Releases Results to LIS
• Simple
  • Fully automated process
  • Easy to learn; Easy to use

• Smart
  • Quality results
  • Reagent monitoring
  • Safe to operate

• Efficient
  • Higher Throughput
  • Reduced Labor
  • More Compact
  • Lower Overall Cost
NHLS & BEC’s South African Solution

Friday at Johannesburg
NHLS & BEC’s South African Solution – Automated PLG

**2005**
- 96 samples per 8 hour shift
- 6 hours of technician time

**Current**
- Transfer of blood and Ab to 12x75mm reaction tube. 20min incubation.
- PrepPlus Series (includes septum pierce, Ab liquid detection, mixing, etc.)
- Lyse RBC using ImmunoPrep reagents
- TQ-Prep (includes timing of incubation and addition of ImmunoPrep reagents)
- Addition of FlowCount
- PrepPlus Series (includes mixing and addition of FlowCount)
- Flow Analysis
  - Epics XL
  - FC500

**2010**
- 288 samples per 8 hour shift
- 2 hours of technician time

**NHLS solution**
- CellMek™
- Automated Sample ID tracking

**2015**
- >300 samples per 8 hour shift
- 5 min technician time

**Sample to Answer Flow Aquios**
- Automated Sample ID tracking
- FC500 MPL
What is it used for?

Leukemia and Lymphoma Diagnosis

<table>
<thead>
<tr>
<th>condition</th>
<th>picture</th>
<th>etiology</th>
<th>cell involved</th>
<th>morphology</th>
<th>clinical presentation</th>
<th>CBC results</th>
<th>demography</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute lymphocytic leukemia (ALL)</td>
<td></td>
<td>chromosomal aberration resulting in abnormal transcription factors that affect development of B and T cells</td>
<td>immature B or T cell (marrow)</td>
<td>condensed chromatin, scant cytoplasm, small nucleoli</td>
<td>stormy onset, symptoms related to depressed marrow function, bone pain, CNS manifestations</td>
<td>anemia, thrombocytopenia, variable WBC’s, &gt;30% lymphoblasts</td>
<td>children.</td>
</tr>
<tr>
<td>chronic lymphocytic leukemia (CLL)</td>
<td></td>
<td>chromosomal deletion or possible somatic hypermutation of postgerminal or naive B cells</td>
<td>peripheral B or T cell (lymph nodes)</td>
<td>smudged cells, condensed chromatin, scant cytoplasm</td>
<td>asymptomatic or nonspecific, LAD, hepatosplenomegaly,</td>
<td>sustained abs. lymphocytosis &gt;5000/ul, low platelets in 20-30%</td>
<td>most common leukemia in adults, twice as common in men.</td>
</tr>
<tr>
<td>acute myelogenous leukemia (AML)</td>
<td><img src="image" alt="Auer Rod in AML" /></td>
<td>oncogenic mutations impede differentiation, accumulating immature myeloid blasts in marrow</td>
<td>immature myeloid lineage cells (marrow)</td>
<td>auer rods (abnormal lysosomes), myeloblasts, monoblast</td>
<td>anemia symptoms, spontaneous bleeding, petechiae and ecchymoses</td>
<td>anemia, neutropenia, thrombocytopenia, &gt;30% myeloblasts, auer rods</td>
<td>adults.</td>
</tr>
<tr>
<td>chronic myeloid leukemia (CML)</td>
<td><img src="image" alt="Philadelphia chromosome" /></td>
<td>tyrosine kinase pathway related chromosomal translocation-Philadelphia chromosome</td>
<td>pluripotent hematopoietic stem cell (marrow)</td>
<td>hypercellular marrow, elevated eosinophils and basophils</td>
<td>insidious onset, mild anemic symptoms, splenomegaly</td>
<td>asx WBC&gt; 50,000, symptomatic WBC&gt; 200,000-1,000,000, some blast forms, increased eosinophils and basophils</td>
<td>ages 20-50, rare in children.</td>
</tr>
</tbody>
</table>
What is it used for?

Interrogating Intra-cellular Signaling Pathways

**KIT COMPOSITION**

**PerFix-nc Kit - PN B10825 - 75 tests**

- Storage at room temperature (18-25°C)
- 12 months shelf life

**Components:**
1. PerFix-nc Buffer 1
2. Fixative reagent
3. PerFix-nc Buffer 2
4. Permeabilizing reagent
5. PerFix-nc Buffer 3
6. Final 10X Solution

An Innovative Tool to Perform SURFACE Plus INTRA Cellular Staining for FLOW CYTOMETRIC Analysis.
What is it used for?

Immune monitoring for Bone Marrow Transplant patients

Recipient
Anticancer drug
Radiation
Alllogeneic bone marrow transplant

Healthy donor
Healthy bone marrow cells removed

Recipient

Naïve T cell
CCR7
CXCR4

Memory T cell
CCR1-10
CXCR3,4,6
CX3CR1

NK cell
CCR1,2,5
CXCR3,4
CX3CR1
XCR1

Neutrophil
CXCR1,2,4

Mast cell
CXCR1,2,3,4

Eosinophil
CCR1,3,4
CXCR4

Basophil
CCR2,3,4
CXCR4

Monocyte
CCR1-5,8
CXCR4
CX3CR1

Dendritic cell
CCR1,5-8
CXCR4

B cell
CCR6,7
CXCR4,5
What is it used for?

Immune monitoring for autoimmune disease patients

The spectrum of autoimmune disease

**Organ Specific Autoimmune Diseases**
- Graves Disease (Thyroid: TSHR Abs, TPO Abs)
- Hashimoto Thyroiditis (Thyroid: TPO Abs, Tg Abs)
- Diabetes Type I (Pancreas: GAD II Abs, IA2 Abs, ICA)
- Goodpasture Syndrome (Kidney: GBM Abs)
- Pernicious Anemia (Stomach: Parietal Cell Abs)
- Primary Biliary Cirrhosis (Liver, Bile: AMAbs)
- Myasthenia Gravis (Muscles: AChR Abs)
- Dermato/Polyarthritis (Skin / Muscles: Jo 1 Abs)
- Vasculitis (Vessels: ANCA)
- Rheumatoid Arthritis (Joints: CRP, RF, RA33 Abs, Sa Abs)
- MCTD (RNP Abs)
- Scleroderma (Scl 70 Abs, CENP Abs, PM/Scl Abs)
- SLE (ANA, Cardiolipin Abs, Beta 2 GP I Abs)

**Multi-systemic Autoimmune Diseases**
- Naïve T cell
  - CCR7
  - CXCR4
- Memory T cell
  - CCR1-10
  - CXCR3,4,6
  - CX3CR1
- NK cell
  - CCR1,2,5
  - CXCR3,4
  - CX3CR1
  - CXCR1
- Neutrophil
  - CXCR1,2,4
- Mast cell
  - CXCR1,2,3,4
- Eosinophil
  - CCR1,3,4
  - CXCR4
- Basophil
  - CCR2,3,4
  - CXCR4
- Monocyte
  - CCR1-5, 8
  - CXCR4
  - CX3CR1
- Dendritic cell
  - CCR1,5-8
  - CXCR4
- B cell
  - CCR6,7
  - CXCR4,5
What is it used for?

Immune monitoring for Solid Organ Transplant patients

Naïve T cell
CCR7
CXCR4

Memory T cell
CCR1-10
CXCR3,4,6
CX3CR1

NK cell
CCR1,2,5
CXCR3,4
CX3CR1
XCR1

Neutrophil
CXCR1,2,4

Mast cell
CXCR1,2,3,4

Eosinophil
CCR1,3,4
CXCR4

Basophil
CCR2,3,4
CXCR4

Monocyte
CCR1-5, 8
CXCR4
CX3CR1

Dendritic cell
CCR1,5-8
CXCR4

B cell
CCR8,7
CXCR4,5
A Unified Approach to Evaluating Cellular Immunotherapy in Solid Organ Transplantation
A Unified Approach to Evaluating Cellular Immunotherapy in Solid Organ Transplantation

Regulatory Cell Products

Recipient before surgery

1. Tregs are collected from the patient receiving the transplant, and white blood cells are collected from the donor. The white cells bear antigens unique to the donor (inset).

2. The cells are cultured with growth factors that prompt multiplication of those Tregs able to recognize donor antigens.

3. Meanwhile, the organ is transplanted, and the patient is given conventional immunosuppressive drugs to prevent rejection.

Recipient after surgery

4. A rich supply of Tregs sensitive to donor antigens is transferred to the recipient.

5. The Tregs suppress or eliminate recipient T cells that are able to attack the graft (inset), thereby protecting the organ and enabling the patient to stop taking immunosuppressive drugs.
“We are what we repeatedly do. Excellence, therefore, is not an act, but a habit.”

Aristotle
Our process begins and ends with the customer

...We’re better together