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- Oncology International Brief Background
- Electroporation
- NanoKnife® System
- NanoKnife® Cases
- The Procedure
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To improve patient health by being the global leader in delivering innovative minimally invasive therapies for peripheral vascular disease and oncology.
AngioDynamics® at a Glance

New CEO: Joseph De Vivo

New International HQ: Amsterdam, The Netherlands

2 Divisions
- Vascular
- Oncology/Surgery

3 Product Groups
- Peripheral Vascular
- Vascular Access
- Oncology/Surgery

Worldwide Presence
- Latham NY - HQ
- 700 Employees
- 5 Operating Locations

Fiscal years run from June to May
- Example FY12: June 2011 – May 2012
AngioDynamics® - Geographic Expansion

US: 88% of WW Sales

- 100+ Person direct sales team
- Strong presence in IR suite
- Large dedicated US Oncology/Surgery team
- Large coverage & penetration through Vascular team

International: 12%

- Selling in 50+ markets through 110+ distributors
- 20 person direct sales team in The Netherlands, UK, Germany and France
- Significant growth opportunities
Committed to R&D

- Significant R&D Investment
  - 10% of revenue in FY11
  - 11 products launched in FY11

- Continued Strong Commitment
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Product Groups - International

**Peripheral Vascular**
- Varicose Veins
- Thrombus Management
- Peripheral Arterial Disease

**Vascular Access**
- Ports
- PICCs
- Dialysis Catheters

**Oncology/Surgery**
- Tumor Ablation
- Surgical Resection
- NanoKnife® Next Gen Ablation
AngioDynamics® International

New Team in 2012

- New Employees 79%

Sales & Marketing Employees at AngioDynamics International at end of June 2011.

January 2012

Ignasi Vivas
Divisional V.P. of Oncology Sales & Marketing, International

Paula Juverdeanu
Marketing Assistant

Peter Dekkers
Regional Sales Director Benelux & Nordics

Dieter Klimke
EMEA Distributor Regional Sales Director

Leon Ng
APAC Regional Sales & Marketing Director

Philip Sousa
Oncology International Marketing Manager

Annet Muetstege
Clinical Affairs Director International

Jolean Tsang
Field Clinical Manager, Oncology, Asia

Bauke Stegenga
Clinical Affairs Project Coordinator International

New Employees 79%

Partners

- Nordics
- Belgium
- The Netherlands
- Luxembourg

Partners

Nordics
Belgium
The Netherlands
Luxembourg
Positioning Products by Disease Stage

Cancer Stage

- **Initial Localized** High OS
  - Resection

- **Loc. Advanced** Medium OS
  - Dry RFA
  - Infused RFA
  - Pre-Chemo

- **Advanced** Low OS
  - IRE
  - Pre-Chemo

Logos:
- Habib
- StarBurst®
- NanoKnife®
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The function of a cell membrane is:

- to separate the intracellular and extracellular environment and
- to control the transport processes between the interior and the exterior of the cell according to the cell needs.

Electroporation is a way to increase cell membrane permeability by subjecting it to an electrical field.
Electroporation:
The process of creating nanopores / “holes” in the cell membrane using an electrical field

Electrical Field

Cell

Permeabilized / Porated Cell Membrane

1. Li et al., PLoS ONE, 6(4): e18831, April 2011
2. Onik et al., Irreversible Electroporation: Implications for Prostate Ablation: Technology in Cancer Research and Treatment 6, 295-300 (2007).
Electroporation

Reversible Electroporation (RE)
- Cell membrane is temporarily “porated” allowing for application
- Application in:
  - Electro-genetherapy
  - Electro-chemotherapy

Irreversible Electroporation (IRE)
- Complete tissue death by means of apoptosis or “apoptosis-mimetic” necrosis

References:
1. Li et al., PLoS ONE, 6(4): e18831, April 2011
2. Onik et al., Irreversible Electroporation: Implications for Prostate Ablation: Technology in Cancer Research and Treatment 6, 295-300 (2007).
Electroporation


<table>
<thead>
<tr>
<th>Electric Field</th>
<th>Pulse Length</th>
<th>Degree of Electroporation</th>
</tr>
</thead>
<tbody>
<tr>
<td>~1kV/cm</td>
<td>~100us</td>
<td>Irreversible</td>
</tr>
<tr>
<td>~50V/cm</td>
<td>~20ms</td>
<td>Reversible</td>
</tr>
<tr>
<td>~1kV/cm</td>
<td></td>
<td>Irreversible</td>
</tr>
<tr>
<td>~50V/cm</td>
<td></td>
<td>Reversible</td>
</tr>
<tr>
<td>~1kV/cm</td>
<td></td>
<td>None</td>
</tr>
</tbody>
</table>

- Thermal
- Irreversible
- Reversible
- None

Destruction of cell membrane
Permeabilized cell membrane
Exposure of cell to electric field

Cell death occurs by apoptosis

- This immune mediated cell death allows
  - Cellular clearance of debris
  - Creates minimal tissue distortion

IRE (Irreversible Electroporation)

Potential Immune system response

Macrophages aid in clearing cell debris - Phagocytosis

References:
1. Meler, JD, Renal Applications of IRE, November 12th 2011, Presentation at Synergy 2011, Miami Florida, USA.
2. Li et al., PLoS ONE, 6(4): e18831, April 2011
3. Lee et al., Technology in Cancer Research and Treatment, 6(4): 287-293, August 2007
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NanoKnife® System Consists Of

- NanoKnife® Generator
- Up to 6 Monopolar electrodes:
  - One Activator RFID Monopolar Electrode
  - Up to five RFID Monopolar Electrodes
- AccuSync® Synchronization Device
NanoKnife® Generator:

- Treatment Planning Software for procedure planning
- USB port to export patient data
- Up to 6 outputs with automatic ‘switching’
- Touchscreen or keyboard input
- Footswitch
- CE Mark
- FDA 510(k) certified
NanoKnife® Electrodes

NanoKnife® RFID Monopolar Electrodes:
- Single Use Disposable Electrodes
- 19 gauge needle with depth markings
- Echogenic needle surface
- 15 cm length
- 25 cm length
- Active electrode length adjustable in 0.5 cm increments from 0 – 4 cm
- Maximum insertion depth = 15 cm

Per procedure:
- 1 x Activator RFID Monopolar Electrode per procedure
- Up to 5 (additional) RFID Monopolar Electrodes
NanoKnife® AccuSync®

AccuSync® Synchronization Device:
- External synchronization device.
- The ECG Trigger Monitor automatically detects the R Wave.
- Provided with each generator.
How the NanoKnife® System Works
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NanoKnife® Cases

Data from: January 16th, 2012

Total Worldwide Cases: 1,017

Liver: 561
Pancreas: 156
Other: 110
Prostate: 83
Kidney: 60
Lung: 47

Other = abdominal, lymph nodes, adrenal gland, spleen, soft tissue next to sacrum, soft tissue next to gallbladder, retroperitoneal, mandible, scrotal
NanoKnife® Cases

Data from: January 16th, 2012

Total International Cases: 222

Liver: 114 cases
Lung: 45 cases
Pancreas: 25 cases
Kidney: 16 cases
Prostate: 14 cases
Other: 8 cases

Other = abdominal, lymph nodes, adrenal gland, spleen, soft tissue next to sacrum, soft tissue next to gallbladder, retroperitoneal,

Surgeons 25%
I.R.’s 75%
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Non-Thermal Ablation\(^1\)

- IRE is a non-thermal ablative technique\(^1\)
  - The electric field created by IRE is devoid of any joule heating

- Application of short pulse, high voltage DC current.

- Rapid series of short electrical pulses

- Cell death occurs in the ablation zone

- Electrodes placed under CT or Ultrasound Guidance\(^2\)

---

1. Li et al., PLoS ONE, 6(4): e18831, April 2011
2. Ball et al., Anesthesia & Analgesia, 110(5): 1305-9, May 2010
Electroporation

Surrounding the ablation zone of Irreversible Electroporation (IRE) there will be an area of reversible electroporation\(^1\).

The area of Reversible Electroporation may have application for Electro-Chemotherapy\(^1,2\) (ECT).

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1. Deodhar et al., AJR, Published Online, 196:W330-W335, March 2011
2. Onik et al., Irreversible Electroporation: Implications for Prostate Ablation: Technology in Cancer Research and Treatment 6, 295-300 (2007).
The NanoKnife® Procedure

- General anaesthetic
  - BIS monitor, arterial line, etc.
  - Muscle relaxant and machine ventilation (Defib. In room)
- Use treatment planning software to plan procedure
- Ensure device is synchronized with ECG (AccuSync®)
- Place needles under CT / US vision
- Activate pulse sequence
- Remove needles & apply band aid
- Patient wakes up and returns home in the same evening or the next morning
The NanoKnife® Procedure
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IRE is a non-thermal technology; hence incomplete treatment secondary to the “heat sink” effect and heat injuries, appear not to be applicable to IRE. ¹

No heat sink effect was evident adjacent to vessels with complete necrosis adjacent and often surrounding patent vasculature.²

1. Deodhar et al., Urology, 77(3): 754-760, 2011
2. Onik et al., Technology in Cancer Research and Treatment, 6(4): 1-6, August 2007
Very precise ablation area on a cellular level – No transition zone.

A cell is either destroyed by IRE or not.¹

IRE produces a well defined region of tissue ablation as a result of loss of integrity of the cell membrane, without areas in which the extent of damage changes gradually, as during thermal ablation.¹
Ablation Precision On A Cellular level


2. NADH-stained porcine renal tissue at 1-h after IRE showing complete cellular death (upper portion of photograph), with a sharp delineation from the untreated tissue (lower portion of photograph).


3. Higher magnification of an ablated area demonstrates a sharp demarcation line between the injured necrotic myocardial tissue (in purple) and the surrounding normal atrial myocardium (original magnification ×10).
Ablation Precision on a Cellular level\textsuperscript{1}

2. Image from: Rubinsky et al., Technology in Cancer Research and Treatment, Vol. 6, N. 1, February 2007

Rubinsky et al., Technology in Cancer Research and Treatment, Vol. 6, N. 1, February 2007:

- Microscopic histology of IRE ablation in the pig liver, 24 hours post IRE. (A) H&E stained section. Margin of ablated area (bottom half) and unaffected area (top half). Focal dark areas are necrotic hepatocytes with calcification. Scale bar 500 micron.\textsuperscript{2}

2. Rubinsky et al., Technology in Cancer Research and Treatment, Vol. 6, N. 1, February 2007
Predictable Ablations\textsuperscript{1,2}

1. NanoKnife Software calculates the programmed ablation zone (based upon mathematical model\textsuperscript{1}), which
2. correlates to the hypo echoic image immediately post-ablation\textsuperscript{2}, and to
3. gross pathology\textsuperscript{2}.

Images from: Rubinsky et al., Technology in Cancer Research and Treatment, Vol. 6, N. 1, February 2007

Mathematical model of ablation zone
Ultrasound post-ablation
Gross pathology of ablation

\textsuperscript{1} Edd et al., Technology in Cancer Research and Treatment, 6(4); 275-286, August 2007
\textsuperscript{2} Rubinsky et al., Technology in Cancer Research and Treatment, Vol. 6, N. 1, February 2007
Predictable Ablations\textsuperscript{1,2}

The NanoKnife\textsuperscript{®} Treatment Planning Software v2.2.0.

\textsuperscript{1} Edd et al., Technology in Cancer Research and Treatment, 6(4); 275-286, August 2007
\textsuperscript{2} Rubinsky et al., Technology in Cancer Research and Treatment, Vol. 6, N. 1, February 2007
Predictable Ablations$^{1,2}$

The NanoKnife® Treatment Planning Software v2.2.0.

---

1. Edd et al., Technology in Cancer Research and Treatment, 6(4); 275-286, August 2007
2. Rubinsky et al., Technology in Cancer Research and Treatment, Vol. 6, N. 1, February 2007
CT and or Ultrasound can be used with NanoKnife¹:
- Pre-procedure,
- During ablation, and
- Post-procedure

MR Imaging:
- May be used pre & post procedure
- NanoKnife® electrodes are not MRI Compatible

References:
2. Rubinsky et al., Technology in Cancer Research and Treatment, Vol. 6, N. 1, February 2007
3. 2010-04-21 Renal – Valley Baptist – Fuentes – Final Needle Placement
4. Meler, JD, Renal Applications of IRE, November 12th 2011, Presentation at Synergy 2011, Miami Florida, USA.
NanoKnife® is non-thermal and will have different imaging characteristics to thermal modalities such as RFA, MWA, and Cryoablation.

Images courtesy of Prof. Ken Thomson, The Alfred Hospital, Melbourne, Australia.
IRE: Vessels and Critical Structures

- No evidence of damage to:
  - Micro and Macro Vasculature\(^1\)
  - Collagen Structures\(^2\)
  - Non-target organ area\(^2\)
  - Bile Ducts\(^2\)
  - Urethra\(^1\)
  - Ejaculatory Ducts\(^1\)
  - Neurovascular Bundle\(^3\)
  - Renal Collecting system\(^4\)

---

1. Onik et al., Series in Biomedical Engineering: Irreversible Electroporation, 235-247, 2010
3. Onik et al., Technology in Cancer Research and Treatment, 6(4) 1-6, August 2007
No evidence of:

- bile leaks,
- strictures, or
- vascular thromboses.
Cellular vs. Non-cellular Tissue Effects

- Cells in ablation zone are irreversibly porated
- Collagenous structures are not affected
  - Intact adventitia & laminae visible at 2 days with no smooth muscle cells present
  - Endothelium largely repopulates at 2 days
  - Smooth muscle repopulated at 2 weeks

---

1. Wong, Jaime; Irreversible Electroporation of the Prostate, November 12th 2011, Presentation at Synergy 2011, Miami Florida, USA.
1. Maor et al., Technology in Cancer Research and Treatment, 6(4), August 2007:

- Top picture: Left common carotid artery seven days after IRE (animal #2). In this picture it is possible to see the scarcity of vascular smooth muscle cells nuclei at the tunica media (arrow A). The elastic fibers morphology is maintained (arrow B).

- Bottom picture: Right common carotid artery of the same animal (animal #2). In this picture it is possible to see the normal density of vascular smooth muscle cells in the tunica media (cells are marked with arrows).
Anaesthesia Considerations

- Relaxant general anesthesia is required for IRE.
- Anesthetic with propofol induction, maintenance with oxygen/air/sevoflurane, and variable opioid regimes usually involving fentanyl or remifentanil.
- Nondepolarizing muscle relaxants used.
- Monitoring with oximetry, noninvasive arterial blood pressure, 5-lead electrocardiograph (ECG), temperature probe, bispectral index, and capnography.
- The majority of the patients had lower-body hot-air blankets.
- If using CT imaging during procedure - attention must be given to patient arm position: neuropraxia.
- Defibrillator in-room
- Before procedure → Twitch test of 0 or 1
Postoperative pain managed with small doses of opioids or simple analgesics in most patients\textsuperscript{1}

- 53.6\% of patients had no pain at all, despite only receiving fentanyl or remifentanil during the procedure.
- Postoperative pain was experienced by 46.4\%;
- Also dependent on whether a patient is suffering from chronic pain before the procedure.

\textsuperscript{1} Ball et al., Anesthesia & Analgesia, 110(5): 1305-9, May 2010
Pain Management

1. Images courtesy of Prof. Ken Thomson, The Alfred Hospital, Melbourne, Australia.
CONTRAINDICATIONS:

- Procedures based on high voltage pulses are not recommended in the following cases:
- Ablation of lesions in the thoracic area in the presence of implanted cardiac pacemakers or defibrillators.
- Ablation of lesions in the vicinity of implanted electronic devices or implanted devices with metal parts.
- Ablation of lesions of the eyes, including the eyelids.
- Patient history of Epilepsy or Cardiac Arrhythmia.
- Recent history of myocardial infarction.

WARNINGS:

Arrhythmia Risk

- Patients with Q-T intervals greater than 550 ms are at an increased risk for inappropriate energy delivery and arrhythmia. Verification of proper function of a synchronization device before initiating energy delivery is essential in these patients.
- Asynchronous energy delivery (240 PPM or 90 PPM modes) might trigger atrial or ventricular fibrillation, especially in patients with established arrhythmias or structural heart disease. Ensure that interventions (defibrillator, etc.) and appropriately trained personnel for dealing with cardiac arrhythmias are readily available.
- Using QRS synchronization devices whose output is not compatible with the specifications listed in this manual may result in ventricular fibrillation.
- Patients with established arrhythmias (i.e. Atrial Fibrillation, PVC’s) should be carefully monitored for proper synchronization during energy delivery.
- Adequate precautions should be taken for patients with implantable electrical devices.
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## NanoKnife® Publications

### Publications based on human data.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson et al., Investigation of the Safety of Irreversible Electroporation in Humans, J Vasc Interv Radiol, 22(5):611-21, May 2011</td>
<td>IRE appears to be safe for human clinical use provided ECG-synchronized delivery is used.</td>
</tr>
<tr>
<td>Ball et al., Irreversible Electroporation: A New Challenge in “Out of Operating Theater” Anesthesia, Anesthesia &amp; Analgesia, 110(5): 1305-9, May 2010</td>
<td>Relaxant general anesthesia is required for IRE of the liver, lung, and kidney. An electrocardiogram synchronizer should be used to minimize the risk of arrhythmias. Attention to the position of the arms is required to maximize CT scan quality but minimize brachial plexus strain. Simple post-operative analgesia is all that is required in most patients.</td>
</tr>
<tr>
<td>Pech et al., Irreversible Electroporation of Renal Cell Carcinoma: A First-in-Man Phase I Clinical Study, Cardiovasc Intervent Radiol, Published online, 15 August 2010</td>
<td>IRE seems to offer a feasible and safe technique by which to treat patients with kidney tumours and could offer some potential advantages over current thermal ablative techniques.</td>
</tr>
<tr>
<td>Brausi et al., Irreversible electroporation (IRE), a novel technique for focal ablation of prostate cancer (PCa): Results of a interim pilot safety study in low risk patients with PCa, Eur Urol Suppl, 10(2):300, March 2011</td>
<td>IRE is a safe procedure for focal therapy in localised low risk PCa. It is relatively simple, mini invasive and effective. Further larger studies with longer follow-up are needed to confirm these preliminary results.</td>
</tr>
<tr>
<td>Onik et al., Irreversible Electroporation: First Patient Experience Focal Therapy of Prostate Cancer, Series in Biomedical Engineering: Irreversible Electroporation, 235-247, 2010</td>
<td>In conclusion, IRE is a new non-thermal ablation modality with significant advantages over heat or cold, based tumor destruction. It’s ability to spare nerves and vessels apparently results in minimal effect on potency making it particularly suited to focal therapy of prostate cancer.</td>
</tr>
<tr>
<td>Narayanan et al., Safety and Efficacy of Irreversible Electroporation in the treatment of primary HCC, Abstract presented at SIR, Chicago, March 2011</td>
<td>Irreversible electroporation of primary liver tumors with the NanoKnife was well tolerated with minimal side effects. Preliminary follow up data appears to be promising with a high percentage of patients having a complete response.</td>
</tr>
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NanoKnife® Summary

**NanoKnife®:**

- Non-thermal ablation, cell death mimics apoptosis.
- System consists of a generator and electrodes, accompanied by an ECG synchronizer.
- “Keeps the patients options open”
- Does not suffer from “heat sink”
- Very precise and predictable ablations
- Can be imaged during procedure with CT / US
- No evidence of damage to stated critical structures.
- Procedure is conducted under general anaesthesia
- Appears to cause less pain to patients
- Therapy would appear to be well tolerated in initial animal and human studies.
NanoKnife® Next Generation Ablation

Thank You