

HYBRiGENiCS

science for life

BIO-CEO Investor Conference

New-York City, 15 February 2011

HYBRIGENICS

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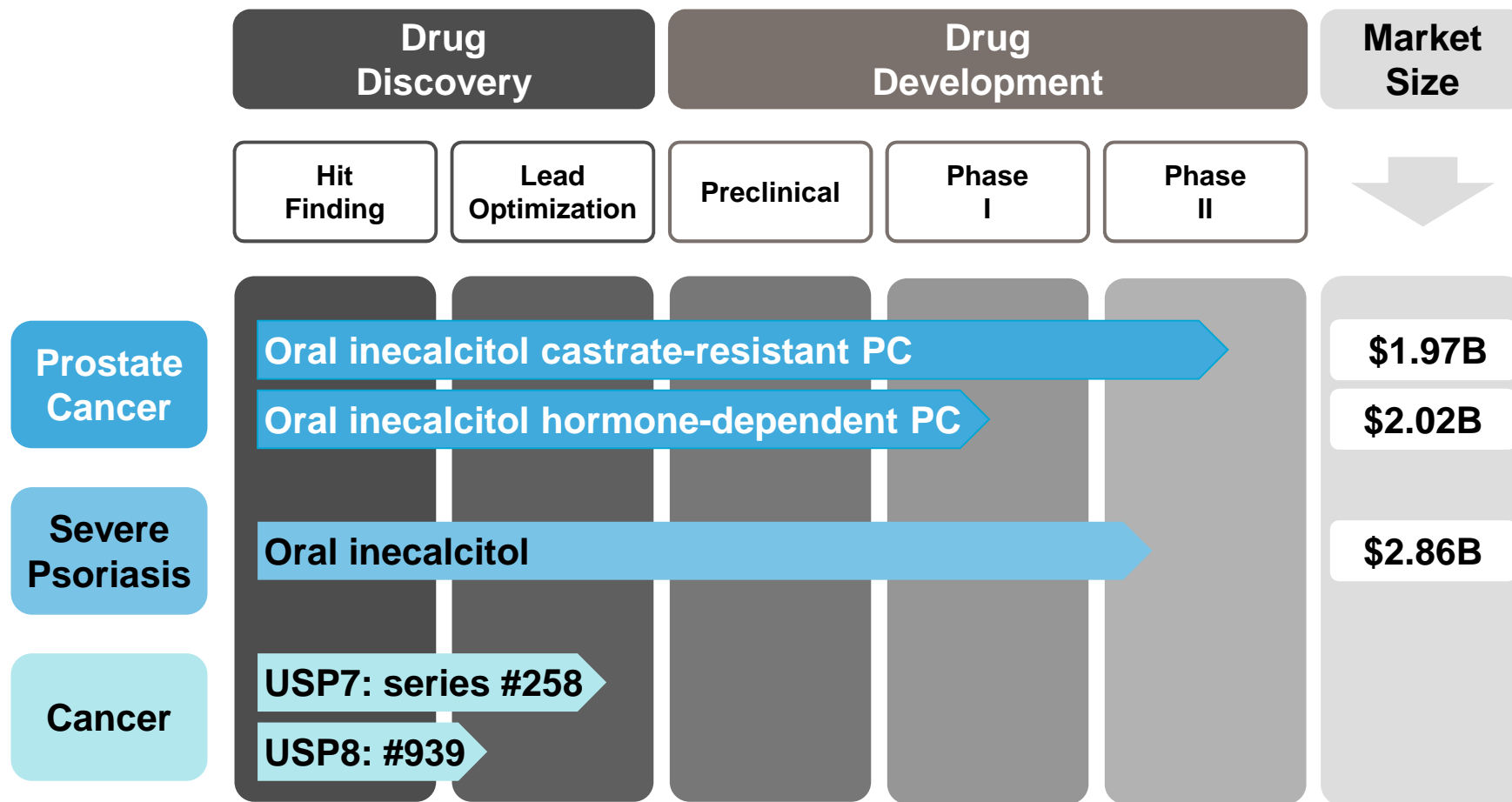
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A biopharmaceutical company with **Pharma** and **Services** activities

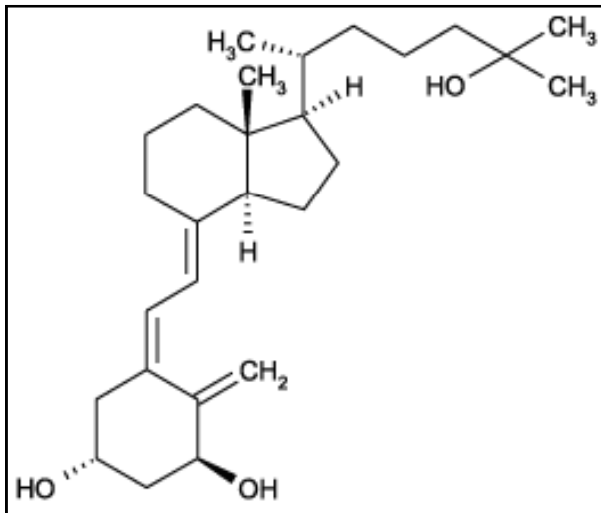
- **Hybrigenics Pharma** focused against cancer
 - Clinical development of **inecalcitol** for prostate cancer
 - Research program focused on **ubiquitin**
- **Hybrigenics Services** focused on proteomics
 - Identification, validation and inhibition of **protein interactions**
 - ISO 9001 certified **Yeast Two-Hybrid** platform
 - Public and private customers from **all life sciences**
 - A fully-owned subsidiary since June 2010
- A **balanced business model** combining:
 - **Recurrent** revenues: **4.54 M€** in 2010
 - Mid- and long-terms **high leverage** pharma R&D projects

Hybrigenics Pharma – a promising pipeline



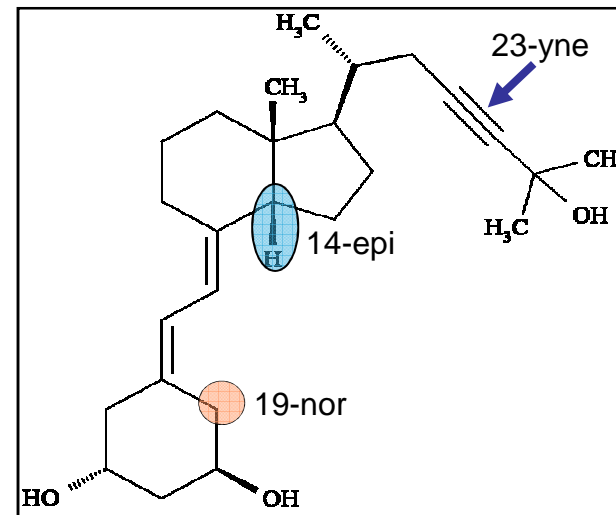
Incalcitol, a vitamin D3 analogue

Calcitriol = 1,25(OH)₂D₃



- › Natural vitamin D3 metabolite
- › Toxicity-limiting hypercalcemic activity, even through the skin

Incalcitol



- › Analogue of calcitriol
- › 10 times more potent on cell lines and 100 times less toxic than calcitriol

Inecalcitol

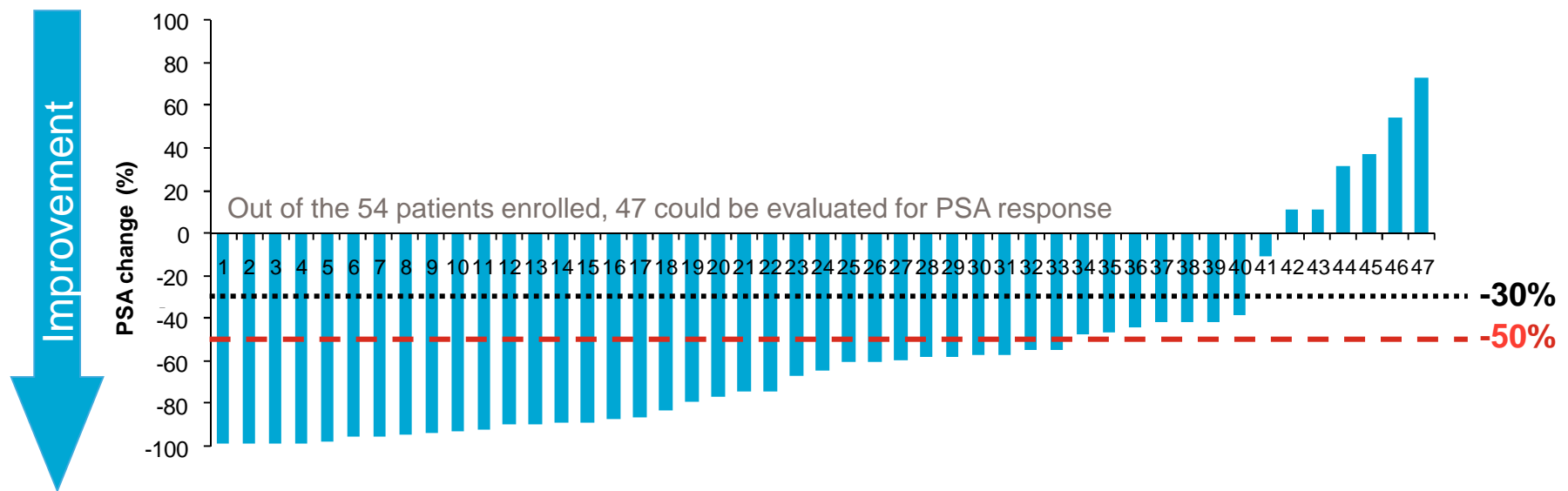
A best in class oral vitamin D analogue

- **Chemically optimized** derivative of calcitriol
- **Selective differential vitamin D effects** due to its un-natural binding to the vitamin D receptor
- **Enhanced potency** against cell proliferation
- **2h half-life** and **no plasma accumulation**
- **Low toxicity** on calcium metabolism
- **Orally** available drug with an **excellent safety** profile
- Phase IIa clinical data with **encouraging PSA response**
- Ideally suited for **1st line treatment of CRPC**

Clinical development of oral **inecalcitol**

- **Phase I** valid for **all oral indications** of **inecalcitol**
- **Phase IIa** in **castrate-resistant prostate cancer**
 - Dose-escalation study in combination to standard **Taxotere[®]** first line chemotherapy for **6 cycles of 3 weeks**
 - **54** castrate-resistant prostate cancer patients
 - Oral doses tested ranged from **40 µg QD to 4 mg BID**
- **Phase IIb** in preparation for the same indication
 - **Pre-IND meeting** agreement with the **FDA**
 - **Scientific Advice** obtained from the **EMA**

Inecalcitol – PSA response rate



- PSA decline >30% within 3 months : 85% of patients
- PSA decline >50% within 3 months : 66% of patients
- PSA decline >50% anytime : 76% of patients

Comparative PSA response rates

Drugs in combination with Taxotere[®]

Drug response ↑

Drug	Taxotere [®] regimen	PSA decline > 30% within 3 months	PSA decline > 50% anytime
Inecalcitol	3w	85%	76%
Custirsen	3w	n/a	58%
Thalidomide	w	n/a	53%
Taxotere[®] alone	3w	67%	45%
Dasatinib	3w	n/a	40%
Atrasentan	3w	35%	23%

- **Inecalcitol** performs markedly better than other therapies under investigation for use in combination with Taxotere[®] in 1st line treatment of castrate-resistant prostate cancer

Conclusions of the Phase IIa study

Excellent safety profile of oral doses up to 4 mg/day for 18 weeks

- No significant changes in calcemia
- The only Serious Adverse Events related to **inecalcitol** were observed at 4 mg twice a day and exclusively linked to hypercalcemia

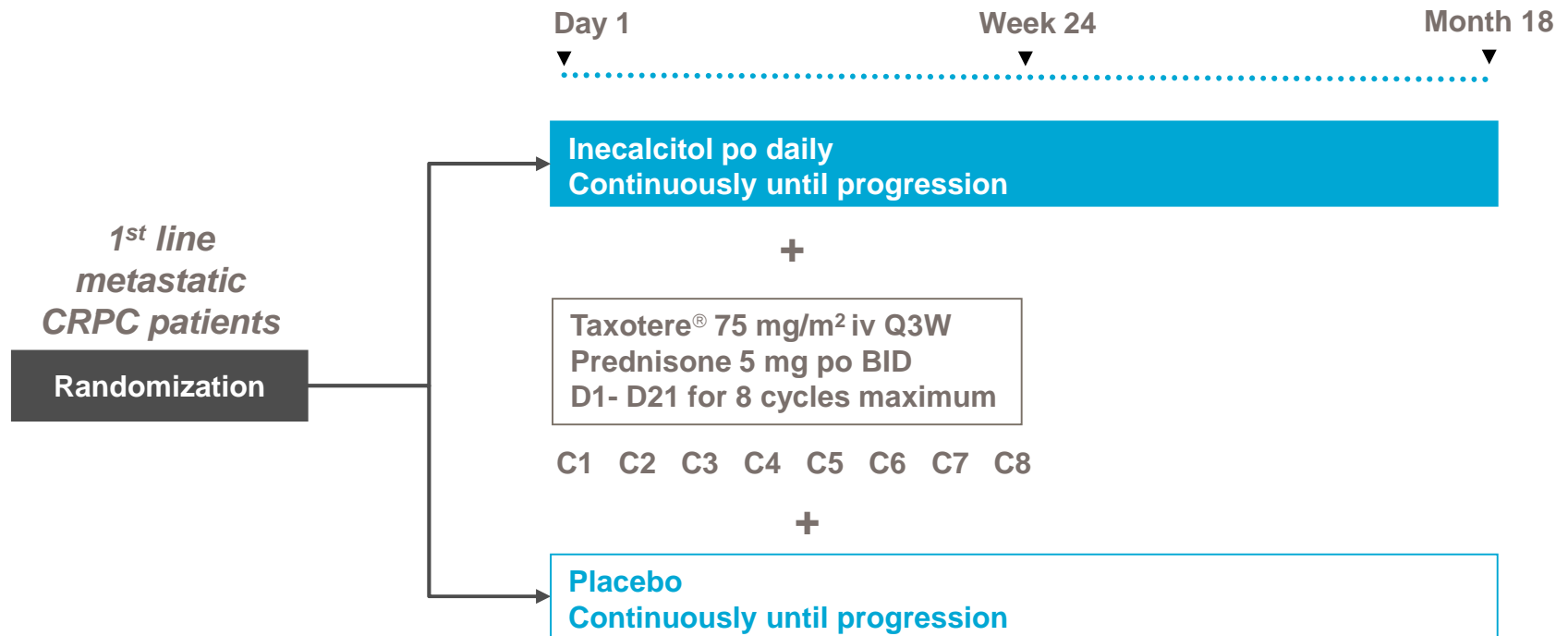
Favorable pharmacokinetic profile without accumulation

- Peak reached between 45 and 90 minutes
- **2h half-life**; no residual **inecalcitol** past 8 hours

Encouraging PSA response rate in 85% of patients

- Strong presumption of efficacy in addition to Taxotere[®] treatment
- Further development in **1st line castrate-resistant prostate cancer**

Phase IIb – Study design



- **Inecalcitol:** daily UNTIL unacceptable toxicity or progression occurs
 - Maximum of 18 months
- **Taxotere® and prednisone regimen:** maximum of 8 cycles of 3 weeks
 - UNLESS unacceptable toxicity or progression occurs

Psoriasis: an opportunity for **inecalcitol**

- Vitamin D analogues are widely prescribed for **mild to moderate psoriasis**, but only by **local** administration on the skin lesions
- Anti-psoriatic vitamin D analogues are toxic by oral administration
- **Severe** psoriasis is characterized by lesions covering a **large body surface**, and local administration is not suitable
- **Injectable anti-TNFalpha** biological therapeutics are prescribed for **severe psoriasis**, representing a **\$2.4 billion market**
- **Systemic administration of inecalcitol by the oral route** may conveniently address the moderate to severe psoriasis market

Inecalcitol intellectual property

- Exclusive worldwide rights for **all therapeutic indications** of **inecalcitol**, protected by a family of granted patents
- Exclusive worldwide rights to a specific **chemical synthesis** of **inecalcitol** protected by a family of granted patents
- **New patents** filed by Hybrigenics in 2009 and 2010
 - Therapeutic use of doses > 1 mg/day of **inecalcitol**: **patent granted**
 - New **14-epi** isomerization synthesis step with significantly increased yield: positive examination recognizing **novelty** and **non-obviousness**
 - New formulations enabling more patient-friendly administration, e.g. **tablets** vs. soft gel capsules: first examination pending

USP inhibitors: an innovative class of anticancer agents

- The **Ubiquitin-Specific Proteases** (USPs) belong to the **Ubiquitin-Proteasome** system, which won recognition by the **2004 Nobel Prize**
- As a proof-of concept, **Velcade[®]**, a **proteasome inhibitor**, is on the market since 2003 for some blood cancers (2009 sales ~\$1.5B)
- Hybrigenics has filed **5 patents** on inhibitors of USPs involved in cancer; the first 2 have already been granted (e.g. HBX 41,108)
- Potential indications of **USP7** and **USP8** inhibitors are **prostate** and **breast** cancers, **melanoma** or **chronic lymphocytic leukemia**
- Results have been validated by the **US National Cancer Institute**
- A research contract with **Servier Laboratories** is addressing another special USP of interest involved in cancer

HYBRIGENICS SERVICES

- Expert in **protein interactions**
 - **Identification** with Yeast Two-Hybrid
 - **Validation** with cell biology
 - **Inhibition** screening with chemical libraries
- **ISO 9001-certified** bioinformatics-backed platform
- A **fully-owned subsidiary** dedicated to fee-for-service
- **750+** customers involved in **all life sciences**
 - From biological **academic** laboratories
 - From **private research** laboratories of pharmaceutical, cosmeceutical, agronomical and biotechnology companies

Catalog of >50 cDNA or genomic Yeast Two-Hybrid libraries

Model organisms



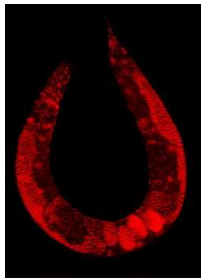
Drosophila



Mice



Zebra fish

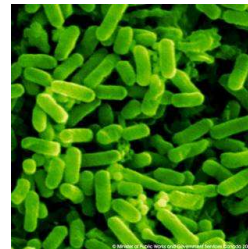


Caenorhabditis elegans

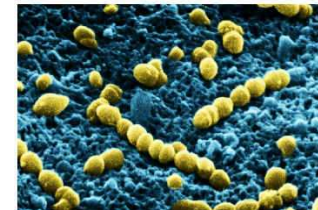


Rat

Bacteria



E. coli



S. aureus



Pneumococcus

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Plants

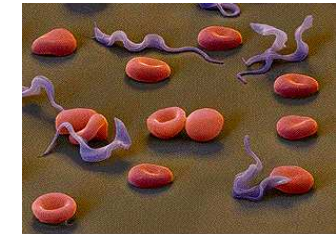


Arabidopsis



Nicotiana

Parasites & hosts



Trypanosoma

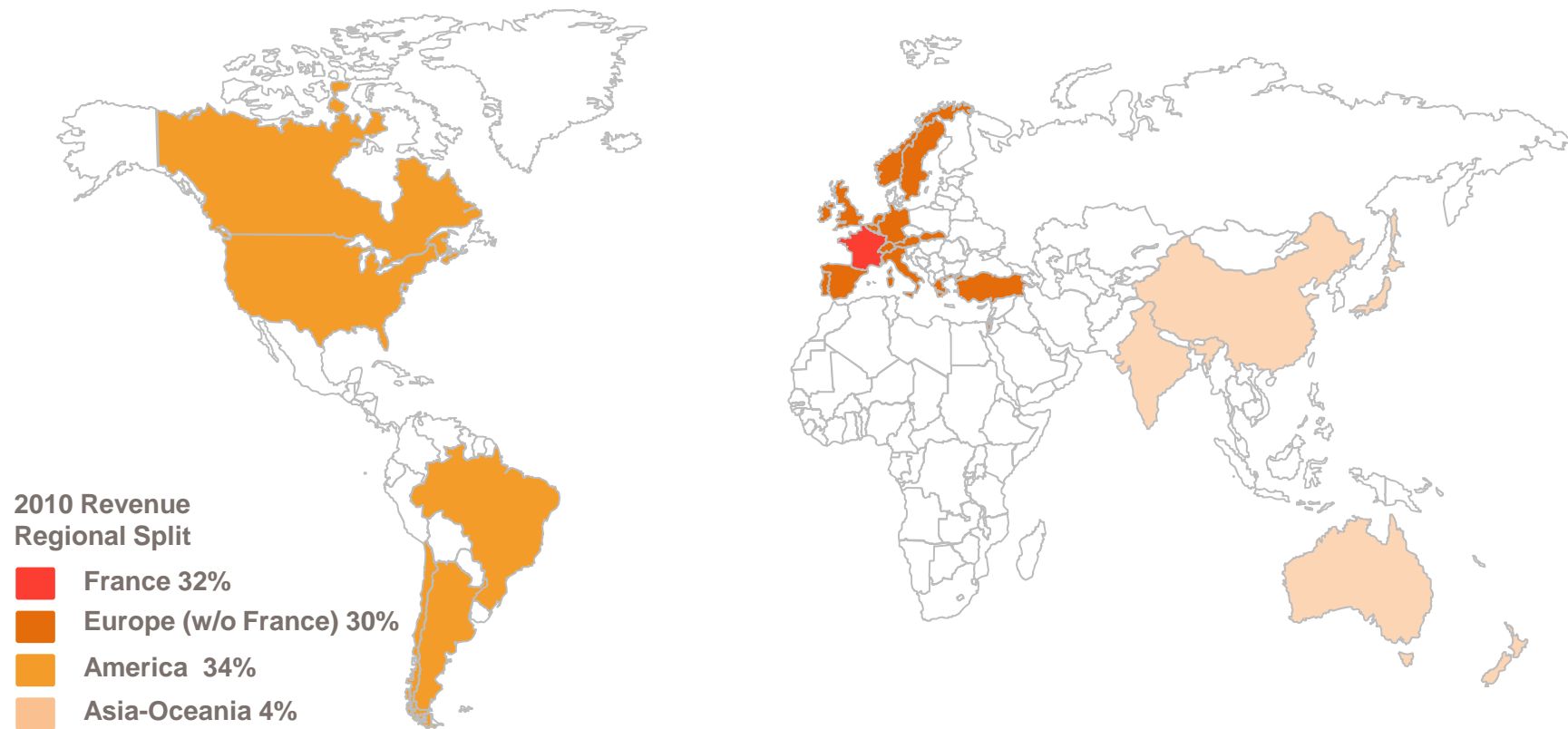


Aedes albopictus
(Chikungunya)

A wide range
of applications

HYBRIGENICS SERVICES

International coverage, recurring revenues



2010 revenues: **3.54 M€ (+6%)**

- 2010 revenues: **3.54 M€**
- **First rate clients**, from **industry (34%)**: Pfizer, L'Oréal, GSK,... and **academia (66%)**: Harvard, John Hopkins, Vanderbilt, Columbia,...
- Cumulative 2004-2010 ISO 9001 **client satisfaction of 93%**
- **Repeat business: 61%** of turnover
- **Low client dependency: < 15%** turnover with the 1st client



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2010 achievements

- Completed Phase IIa study of inecalcitol in prostate cancer
- Identified novel USP inhibitors
- Subsidiarized Hybrigenics Services
- Enhanced IP protection of inecalcitol

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2011-2012 corporate development plan

- Cash generation by Hybrigenics Services
- Partnering of inecalcitol with co-development agreement
- Initiate efficacy Phase IIb Proof-of-Concept study of inecalcitol in prostate cancer and severe psoriasis

**A clear strategy and a mitigated risk profile
with short to mid-term high leverage milestones**

Science for life