Subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, USA

Novel Inhibitors of Tryptophan Metabolism as Cancer Immunotherapies

Alan Wise

CEO
IOmet Pharma – Company Background 2010

• Company founded in 2008 under the name ‘TPP Global Development’ by co-founders Dr Tom Brown (CEO) and Peter Trill (CFO)
  • Both had significant experience (>10 years) of working in Healthcare Investments Sector

• Series A finance raise in April 2010 (£9.6 m)
  • Strong investor network

• Edinburgh-based biotechnology company with business model to identify novel drug targets and develop novel drugs

• Operating in a virtual manner ie no wet labs
  • All of the research is contracted out / partnered
Virtual Pharma

or
IOmet Pharma 2010 - Therapeutic Focus Areas

- Neuro-Degenerative Disorders
  - Orphan Drug Indications
- Immunology
  - Inflammation
- Oncology
  - Tumour Micro Environment
  - Cancer Metabolism
Pre-Clinical Focus:

- Identify/assess novel IP
- Develop clean, validated leads for out-licensing / further development

Acquisition / Licensing Deal with Pharma

IOmet development activity

Academia

Basic Research

Drug Discovery

Drug Development

Clinical Trials

Approval

VALUE
IOmet Target Selection Criteria

- Strong target/pathway validation
- Novel or best-in-class ideas with direct disease relevance
- Freedom to operate & secure IP
- Is it commercially attractive i.e., will there be a customer for the asset?

>300 ideas top level reviewed
158 ideas reviewed in-depth
Active portfolio of <5 projects
Virtual Biotech Model

Internally ~ 5-10 FTEs

CROs: 25-30 FTEs
IOmet Pharma – 2016 Version

- Now based at the Edinburgh Bioquarter
  - Renamed ‘IOmet Pharma’ 4Q2014 to better reflect scientific focus
- Pre-clinical R&D pipeline focused on cancer immunotherapy and cancer metabolism
- Wholly-owned subsidiary of MSD as of 11 Jan 2016
Cancer Immunotherapy

This year marks a turning point in cancer, as long-sought efforts to unleash the immune system against tumors are paying off—even if the future remains a question mark.

History’s path is uncharted when it’s not yet past but present, when we are still standing in the middle of it. That’s what made Science’s selection of this year’s Breakthrough of the Year such a topic of internal debate, even anxiety. In celebrating cancer immunotherapy—harnessing the immune system to battle tumors—did we risk hyping an approach whose ultimate impact remains unknown? Were we irresponsible to label as a breakthrough a strategy that has touched a tiny fraction of cancer patients and helped only some of them? What do we mean when we call something a breakthrough, anyway?

Ultimately, we concluded, cancer immunotherapy passes the test. It does so because this year, clinical trials have cemented its potential in patients and swayed even the skeptics. The field hums with stories of lives extended: the woman with a grapefruit-size tumor in her lung from melanoma, alive and healthy 13 years later; the 6-year-old near death from leukemia, now in third grade and in remission; the man with metastatic kidney cancer whose disease continued fading away even after treatment stopped.

As the anecdotes coalesce into data, there’s another layer, too, a sense of paradigms shifting. Immunotherapy marks an entirely different way of treating cancer—by targeting the immune system, not the tumor itself. Oncologists, a grounded-in-reality bunch, say a corner has been turned and we won’t be going back.

With much pressure these days to transform biological insights into lifesaving drugs, there’s a lesson to be learned from immunotherapy’s successes: They emerged from a careful decoding of basic biology that spanned many years. The early steps were taken by cancer immunologist James Allison, now at the University of Texas MD Anderson Cancer Center in Houston. In the late 1980s, French researchers who weren’t thinking about cancer at all identified a new protein receptor on the surface of T cells, called cytotoxic T-lymphocyte antigen 4, or CTLA-4. Allison found that CTLA-4 puts the brakes on T cells, preventing them from launching full-out immune attacks.

He wondered whether blocking the blocker—the CTLA-4 molecule—would set the immune system free to destroy cancer.

Allison’s rationale was untested.

He and his colleagues changed the conversation, in the words of one cancer researcher, “to consider immunosuppression as the focal point, and manipulation of immunosuppression as the target.”

Doing so took time. CTLA-4 was discovered in 1987. In 1996, Allison published a paper in Science showing that antibodies against CTLA-4 erased tumors in mice. Seek and destroy. Instead of targeting tumors directly, cancer immunotherapy enables the immune system to attack them. Here, an antibody (pink) blocks a receptor (purple) found on T cells (gray), setting off a chain reaction that leads to an assault on
Paradigm Shift in Survival Prospects

**Metastatic Melanoma**

Yervoy (α-CTLA4)
Hodi et al, NEJM, 2010

**Significant shift in response:**
- ORR Yervoy alone: 19%
- ORR Yervoy + Opdivo: 58%
- 38% patient discontinued due to SAEs

**Advanced Melanoma**

Yervoy (α-CTLA4) + Opdivo (α-PD-1)
Postow et al, NEJM, 2015

**Opportunity:**
- Reach non-responding patients
- Increase depth & duration of responses
- Safer & more tolerable combination than with α-CTLA4
IDO1 & TDO: Key Players in Cancer Immune Suppression

Increased IDO1 and/or TDO activity in tumour microenvironment suppresses host immune response to tumour
TDO/IDO Inhibitors: Tipping the Balance

Tumour micro-environment promotes proliferation of cells that disarm the body’s immune system = tumour immune evasion and growth

TDO or IDO inhibition activates immune effector cells, relieving the brake on the immune system, triggering killing of cancer cells
Rationale for Inhibition of Both IDO1 & TDO

- IDO1 and/or TDO commonly upregulated in cancer cells
- Inhibit IDO1 / TDO activity – reduce Kyn levels – immune system can eliminate tumour
- Targeting both enzymes offers potential to:
  - Increase addressable patient population
  - Enhance depth & duration of response
IDO1 and TDO2 expression define distinct cancer groups
IDO1 is highly correlated with PD-L1

Each dot represents a gene; x-axis is correlation with PD-L1 in 16k human tumor samples; y-axis is correlation with immune infiltrate signature
TDO is also correlated with PDL1 and the immune infiltrate signature
IDO1 & TDO Inhibitors – Extensive IO Combination Opportunities

Multiple IDO1 combination clinical studies ongoing
IDO1/TDO Inhibitors: A Highly Competitive Field

- **Merck**
  - Dual IDO/TDO Discovery
- **Incyte**
  - Epacadostat (Ph II-III)
- **Bristol-Myers Squibb**
  - Flexus F-001287: Ph I
  - GDC-0919 (Ph Ib)
- **Genentech**
  - A Member of the Roche Group
- **Curadev**
  - Dual IDO/TDO Discovery
- **Roche**
  - PF-06840003 in Ph I (glioma)
- **iTeos Therapeutics**
  - IDO1selective
  - TDO selective
- **Huya**
  - Discovery
- **Vertex**
  - Discovery
- **Merck**
  - Discovery
- **Kyorowa Kirin**
  - Discovery
Epacadostat Demonstrates Encouraging Clinical Responses in Combination with Pembrolizumab

Epacadostat, an IDO1 selective inhibitor, demonstrates encouraging efficacy in a variety of tumor types in combination with pembrolizumab with a safety profile similar to pembrolizumab monotherapy in Phase II.
IOmet Pharma – Early Drug Discovery Collaboration with Leading UK Academic Drug Discovery Centre

• Target Development Fund established with

via research funding from

• 2011 initiated hit identification efforts with the DDU at the enzyme TDO, a new cancer immunotherapy target
  • Access to DDU compound collection
  • Access to world-class ‘hands-on’ drug discovery expertise
IDO1, TDO & Dual Inhibitor Programs Overview

Cancer cell assays measuring compound inhibition of endogenous IDO1 or TDO activity.
Female C57BL/6 mice inoculated subcutaneously with 5x10^6 PAN02 mouse pancreatic adenocarcinoma cells, n = 10 per cohort. Dosing initiated when tumors reached ~90 mm^3. Mice dosed @ 100 mg/kg BID all compounds.
**IOmet IDO1-Selective Inhibitor – Outstanding Efficacy in Combination with Chemotherapy**

Female C57BL/6 mice inoculated subcutaneously with $5 \times 10^6$ PAN02 mouse pancreatic adenocarcinoma cells, n = 10 per cohort. Dosing initiated 6 days post inoculation.

- IDO1 Inhibitor: 100 mg/kg BID
- Gemcitabine: 80 mg/kg IP Q3D4
- Abraxane: 15 mg/kg IV Q3D4

**Tumour Growth Control**

- **Vehicle**
- **IOmet |IDO1 Inhibitor 1**
- **Gem / Abr**
- **IOmet |IDO1 Inhibitor 1 + Gem / Abr**

* **** p < 0.0001, 2-way ANOVA, vs Vehicle

* **** p < 0.0001, 1-way ANOVA
Oral dosing with IOmet TDO or Dual Inhibitor causes profound and sustained reduction in plasma kynurenine

**TDO Inhibitor**
Rat Plasma Kynurenine Levels

**Dual IDO1/TDO Inhibitor**
Rat Plasma Kynurenine Levels

- 1 mg/kg
- 3 mg/kg
- 10 mg/kg
- 30 mg/kg

- 10 mg/kg
- 30 mg/kg
- 100 mg/kg
• Provide significant *in vivo* efficacy in mouse tumour studies as single agents and in combination with chemotherapeutics

• Show strong PK/PD relationships

• Demonstrate clean profile in broad panel of *in vitro* safety assays

• Possess characteristics strongly supportive of clinical development
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