R&D Meeting 2007

December 13th, 2007
Astellas Pharma Inc.
Cautionary statement regarding forward-looking information

This material includes forward-looking statements based on assumptions and beliefs in light of the information currently available to management and subject to significant risks and uncertainties. Actual financial results may differ materially depending on a number of factors including adverse economic conditions, currency exchange rate fluctuations, adverse legislative and regulatory developments, delays in new product launch, pricing and product initiatives of competitors, the inability of the company to market existing and new products effectively, interruptions in production, infringements of the company’s intellectual property rights and the adverse outcome of material litigation.

This material contains information on pharmaceuticals (including compounds under development), but this information is not intended to make any representations or advertisements regarding the efficacy or effectiveness of these preparations nor provide medical advice of any kind.
Today’s Agenda

1. Overview of Astellas R&D Activities
2. Pipeline Products
   - **Urology**: YM905 (Vesicare)  
     YM178
   - **Cardiovascular**: YM150  
     RSD1235 (vernakalant)  
     YM758
   - **Diabetes**: YM543 / ASP1941
   - **Infectious diseases**: Telavancin
   - **Transplantation**: Anti-CD40 antibody
3. Acquisition of Agensys
Overview of Astellas R&D Activities
Toward Generating New Products

- Reinforcing research function
- Early launch of antibody business
- Progress in development pipeline
Global Research Organization

Drug discovery research

- Molecular Medicine Research Labs.
- Fermentation Research Labs.
- Chemistry Research Labs.
- Analysis & Pharmacokinetics Research Labs.
- Pharmacology Research Labs.

Preclinical research

- Drug Metabolism Research Labs.
- Drug Safety Research Labs.
- Applied Pharmacology Research Labs.
- APERD

Japan

Europe

US

Agensys (antibody)

*Closing is planned by the end of Dec. 2007
New Research Facilities in Tsukuba

- New facilities under construction as a part of reorganization of research function (completion in August 2008 (scheduled), total cost: approx. ¥30 billion)
- After completion of the construction, drug discovery research and preclinical research function will be located in Tsukuba area* and Kashima area, respectively.
- *Laboratories in Tsukuba area after the completion of new facilities:
  - Tokodai area: Fermentation Research Labs.

Pursue speeding up and high quality of activities of drug discovery
Global R&D Organization

**Japan**
- Tsukuba
- Osaka

**EU**
- Leiderdorp, NL (APERD)

**USA**
- Skokie, IL (ARIA)
- Durham, NC (Urogenix)
- Santa Monica, CA (Agensys)**

- Deerfield, IL (APUS)

*including clinical development in Asia

**closing date of acquisition of Agensys is planned by the end of Dec. 2007*
Establish New Core Technology: Antibody Drugs

In-house research
Molecular Medicine Research Labs. leads the in-house antibody drug discovery.

Product in-licensing

<table>
<thead>
<tr>
<th>Originator</th>
<th>Target indications</th>
<th>Territory</th>
<th>CD40 antagonistic mAb (Jan. 2007)</th>
<th>Worldwide</th>
<th>Kirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBL</td>
<td>Rheumatoid arthritis</td>
<td>Worldwide</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Originator</th>
<th>Target indications</th>
<th>Territory</th>
<th>Anti-human osteopontin antibody (Mar. 2006)</th>
<th>Worldwide</th>
<th>IBL</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBL</td>
<td>Prophylaxis of organ rejection associated with organ transplant</td>
<td>Worldwide</td>
<td>CD40 antagonistic mAb (Jan. 2007)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Technology in-licensing

<table>
<thead>
<tr>
<th>Originator</th>
<th>Granted rights</th>
<th></th>
<th>MorphoSys AG (Mar. 2007)</th>
<th>Access to MorphoSys’ antibody library</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regeneron (Mar. 2007)</td>
<td>Utilization of VelocImmune technology to discover human mAb</td>
<td></td>
<td>Regeneron (Mar. 2007)</td>
<td>Utilization of VelocImmune technology to discover human mAb</td>
</tr>
</tbody>
</table>

Acquisition of Agensys, Inc. - Early launch of antibody drugs
Advanced technology platform and pipeline in cancer, GMP certificated antibody production (CMC)
Progress of Pipeline in 2007 (Jan. - Dec.) (1)

1. Number of Projects: P1 + P0 (as of Dec. 2007)

   31 projects

2. Number of Projects with ‘ASP’ code
   (projects entered development phase since April 2005)

   | P2 or advanced | in-licensed       | ASP3550 (prostate cancer) |
   |               |                  | ASP0485 (immunosuppressant) |
   |               |                  | ASP1585 (hyperphosphatemia) |
   |               |                  | ASP8825 (RLS, PDN)*        |
   |               |                  | telavancin (injectable antibiotic) |

   | in-house       |                  | ASP2151                      |
   |               |                  | (herpes zoster, genital herpes) |

   | P1 + P0        | in-licensed       | 4 projects                   |
   |               |                  |                              |

   | in-house**     |                  | 21 projects                  |

   ** including co-development
Progress of Pipeline in 2007 (Jan.- Dec.) (2)

■ Approval
- Advagraf (EU/immunosuppressant (modified release))
- Celecox (JPN/COX2 inhibitor)
- Geninax (JPN/oral quinolone antibiotic)
- Starsis combination therapy with biganides (JPN/ type 2 diabetes)

■ Filing
- YM177 (JPN/ low back pain, etc.)
- YM617 (JPN/ lower urinary tract syndrome with male patients)
- CVT-3146 (US/ pharmacologic stress imaging agent)
- telavancin (EU/ complicated skin and soft tissue infections)

■ P2b completed in major projects: Favorable results
- YM150 (VTE) P2b in Europe
- YM178 (OAB) P2b in Europe

VTE: prevention of venous thromboembolism
OAB: overactive bladder
■ Steady progress in development

YM155 P2 trial in NHL, co-administration therapy for HPRC, etc.

■ New projects initiating P2

ASP2151 (herpes zoster, genital herpes), YM543 (type 2 diabetes)
ASP8825 (RLS*, PDN**), ASP1585 (hyperphosphatemia)
ASP0485 (immunosuppressant)
ASP3550 (prostate cancer)
solifenacin/tamsulosin (LUTs associated with BPH), etc.

*RLS: restless legs syndrome
**PDN: painful diabetic neuropathy

■ Response to the Authorities

  => Response submitted
  (Liver: July 2007, Kidney: Sep. 2007)
- YM311, FG-4592: All clinical trials are on hold by instruction of FDA
  => Response to be submitted during 2007
# Major Pipeline List

<table>
<thead>
<tr>
<th>Filed</th>
<th>Urology</th>
<th>CV</th>
<th>Diabetes</th>
<th>Infectious diseases</th>
<th>Transplant (Immunology / Inflammatory)</th>
<th>Cancer, GI, CNS, Bone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YM617(J)*</td>
<td>YM086 (J)*</td>
<td>YM086 (J)*</td>
<td>telavancin</td>
<td>FK506MR* (J,U)</td>
<td>YM060(J)</td>
</tr>
<tr>
<td></td>
<td>RSD1235(U)</td>
<td>YM026 (J)*</td>
<td>YM026 (J)*</td>
<td>cSSSI(U,E)</td>
<td>FK506(U)* (MMF)</td>
<td>YM529(J)</td>
</tr>
<tr>
<td></td>
<td>CVT-3146(U)</td>
<td></td>
<td></td>
<td>FK463(E)</td>
<td>YM177(J)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FK463(U)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P3</td>
<td>YM617(U)*</td>
<td></td>
<td></td>
<td>telavancin</td>
<td>FK506(J)* (MG / UC)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HAP(U,E)</td>
<td>YM177(J)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FK506(U)* (cream)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>YM199B(J)*</td>
<td></td>
</tr>
<tr>
<td>P2</td>
<td>YM178(J,E)</td>
<td>YM150(J**,E,U)</td>
<td>YM543(E)</td>
<td>ASP2151(J,U)</td>
<td>YM974(J)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>solifenacin/ tamsulosin(E)</td>
<td>YM311(J,E)</td>
<td></td>
<td></td>
<td>YM978(J)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ASP3550(J)</td>
<td>YM533(J)*</td>
<td></td>
<td>ASP0485(U,E)</td>
<td>ASP8825(J)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ASP1585(J)</td>
<td></td>
<td></td>
<td></td>
<td>YM060(E)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>YM443(U)</td>
<td></td>
</tr>
</tbody>
</table>

Area: J: Japan, U: US, E: Europe / * Additional indication or Additional formulation, etc. ** YM150(J): international trial in Japan and Asia
- Urology -

YM905 (Vesicare)
Efficacy for Urgency
Accumulating Evidence of Vesicare

- LAUNCH-2005
- STAR
- VOLT, VERSUS
- SUNRISE, VENUS (Urgency)
- SOLAR (underway, BT*)
- VIBRANT (underway, QOL)

*BT: Bladder Training
ICS Definition of OAB

Urgency, with or without urge incontinence, usually with frequency and nocturia

ICS: International Continence Society, OAB: Overactive Bladder

SUNRISE: Efficacy for Urgency Episode
Solifenacin for Urgency of OAB in a Rising Dose Efficacy Trial

VISITS
1: Screening
2: Baseline
3: Primary assessment
4: Option to increase dose
5: Final

Placebo (P)
3:1 ratio

Solifenacin 5mg

Dose increase on demand
Randomization

ASSESSMENTS
PRI
Treatment Period

Week -2 0 1 2 4 8 12 Week 16

Solifenacin 5mg + 5mg
Solifenacin 5mg + P
Solifenacin 5mg
Placebo + Placebo
Placebo + Placebo
Placebo

SUNRISE: Efficacy for Urgency Episodes

Change in mean number of urgency episodes (graded as PPIUS* 3 or 4) per 24 hrs at endpoint

Est. Diff. = -1.0
P < 0.0001

Mean baseline: 5.5 5.1
Endpoint: 3.7 2.5

Solifenacin
Placebo

*PPIUS: Patient Perception of Intensity of Urgency Scale

Cardozo L et al Int Urogynecol J 2006; 17(Suppl 2): S88 Abstr 052
**VENUS: Efficacy for Urgency Episode**

**VESlcare® Efficacy and Safety in Patients with Urgency Study**

<table>
<thead>
<tr>
<th>Week</th>
<th>Assessments &amp; Flexible Dosing</th>
<th>Assessments &amp; Flexible Dosing</th>
<th>Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>Washout</td>
<td>n=372</td>
<td>Solifenacin 5 mg</td>
</tr>
<tr>
<td>0*</td>
<td>Solifenacin 5 mg</td>
<td>Solifenacin 5 mg</td>
<td>Solifenacin 5 + 5 mg</td>
</tr>
<tr>
<td>1</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>4†</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>8†</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>12†</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

*Patients completed diaries for 7 consecutive days prior to the study visit.
†Patients completed diaries for 3 consecutive days prior to each study visit.

Serels S et al Urology 2006; 68(Suppl 5a): 72 MP-04.11
VENUS: Efficacy for Improving Warning Time*

First antimuscarinic agent at licensed dose to significantly improve warning time, allowing patients additional time to find a toilet

Median of Warning Time

* P<0.0321

Increase in Warning Time by solifenacin = 186.4 sec

Mean of Warning Time

Solifenacin (n=280)
Placebo (n=272)

Baseline
Additional Warning Time

Toglia M et al Neurourol Urodyn 2006; 25(6); 655 Abstr 123

*Warning Time: time from the first sensation of urgency to voiding
- Urology -
YM178
Indications: Urinary frequency, urgency, urge incontinence associated with overactive bladder

Mechanism of action: β3 receptor agonist

Formulation: Oral

Status:

Europe and US: Completed End of P2 Meeting with health care authorities in the US and Europe in November

Start P3 in 1st half of FY2008

Japan: P2
YM178  P2a results

Study design

Purpose: Evaluate the efficacy, safety and tolerability of YM178 in patients with OAB

Treatment period: 4 weeks

Efficacy results

YM178 showed statistically significant difference against placebo among all endpoints

<Primary endpoints> Urinary frequency
<Secondary endpoints>
  Urgency, urge incontinence, volume void / micturition

Safety and tolerability results

Treatment with YM178 was well tolerated

Publication of P2a results

To be published at the major urology conference in 2008
YM178 P2b results

- **Study design**
  - Purpose: Evaluate the efficacy, safety and tolerability of YM178 in patients with OAB
  - Dose finding study
  - Treatment period: 12 weeks

- **P2b results in Europe**
  - YM178 showed statistically significant difference against placebo on the primary endpoint, reduction in mean number of micturitions/24hrs, as well as secondary endpoints
  - Dose dependency shown
  - Treatment with YM178 was well tolerated
- Cardiovascular -
YM150
Direct Factor Xa inhibitor YM150 for prevention of VTE in patients undergoing elective hip replacement

ONYX-2 study
Oral direct iNhibition by Ym150 of factor Xa

Bengt I. Eriksson
on behalf of Giancarlo Agnelli, Michael R. Lassen, Martin H. Prins, and Alexander G.G. Turpie
and the ONYX-2 investigators
ASH, Atlanta, 10th December 2007
Study Objectives

- To identify the optimal therapeutic dose

  - Evaluation of the efficacy of different doses of YM150 in subjects undergoing elective primary hip replacement surgery
  - Evaluation of the safety of different doses of YM150 in the target population

Source: 2007 American Society of Hematology
Primary Endpoint

Primary **Efficacy** endpoint

Total VTE up to Day 7-10 as the composite of
- DVT detected by bilateral venography and/or
- Symptomatic DVT and/or
- Pulmonary embolism and/or
- Death due to any cause during treatment

Primary **Safety** endpoint

Incidence of Major bleeding during 7-10 days treatment

Source: 2007 American Society of Hematology
ONYX-2 Design

**In hospital treatment**
- YM 150 5 mg
- YM 150 10 mg
- YM 150 30 mg
- YM 150 60 mg
- YM 150 120 mg
- enoxaparin 40 mg

**Home treatment**

**Follow up**

**Day 7 – 10**
- Benchmark: Open label enoxaparin
  - Started 12 h pre-operatively

**Day 33-38**
- Mandatory bilateral venography

**Day 61-68**
- End of treatment

81 sites; 17 European countries
Patients per group: 110 evaluable venograms

Source: 2007 American Society of Hematology
## Total VTE up to Day 7-10

### Primary efficacy endpoint

<table>
<thead>
<tr>
<th></th>
<th>YM150 5 mg n = 117</th>
<th>YM150 10 mg n = 120</th>
<th>YM150 30 mg n = 114</th>
<th>YM150 60 mg n = 120</th>
<th>YM150 120 mg n = 110</th>
<th>Enoxaparin 40 mg n = 127</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI</td>
<td>32 (27.4%)</td>
<td>38 (31.7%)</td>
<td>22 (19.3%)</td>
<td>16 (13.3%)</td>
<td>16 (14.5%)</td>
<td>24 (18.9%)</td>
</tr>
<tr>
<td></td>
<td>20.0, 36.1</td>
<td>23.5, 40.7</td>
<td>12.9, 27.2</td>
<td>7.8, 20.5</td>
<td>8.5, 22.4</td>
<td>12.5, 26.4</td>
</tr>
<tr>
<td><strong>DVT by venography</strong></td>
<td>31 (26.5%)</td>
<td>38 (31.7%)</td>
<td>22 (19.3%)</td>
<td>16 (13.3%)</td>
<td>15 (13.6%)</td>
<td>24 (18.9%)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>1 (0.9%)</td>
<td>1 (0.8%)</td>
<td>0 (0.0%)</td>
<td>1 (0.8%)</td>
<td>1 (0.9%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (0.9%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

Source: 2007 American Society of Hematology
# Major bleed up to Day 7-10

**Primary safety endpoint**

<table>
<thead>
<tr>
<th></th>
<th>YM150 5 mg n= 158</th>
<th>YM150 10 mg n= 161</th>
<th>YM150 30 mg n= 156</th>
<th>YM150 60 mg n= 163</th>
<th>YM150 120 mg n= 156</th>
<th>Enoxaparin 40 mg n= 166</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Per cent</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.6</td>
<td>0</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Source: 2007 American Society of Hematology
Any bleed (%) up to Day 7-10

Major +CRNM bleeds YM150 dose trend (5 mg -120 mg): p = 0.3735

All bleeds YM150 dose trend (5 mg -120 mg): p = 0.0025

Source: 2007 American Society of Hematology
Patients with ALT > 3 x ULN and Bilirubin > 2 x ULN

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>10 mg</td>
<td>Normalized on treatment</td>
</tr>
<tr>
<td>D</td>
<td>10 mg</td>
<td>Normalized on treatment</td>
</tr>
<tr>
<td>I</td>
<td>10 mg</td>
<td>Normalized after cholecystectomy</td>
</tr>
<tr>
<td>G</td>
<td>60 mg</td>
<td>Normalized on treatment</td>
</tr>
<tr>
<td>L</td>
<td>120 mg</td>
<td>Normalized on treatment</td>
</tr>
</tbody>
</table>

Source: 2007 American Society of Hematology
Conclusions

- VTE up to Day 7-10 decreased significantly with increasing dose of YM150 (p=0.0002)

- YM150 at doses of 30-120 mg appears to be effective

- YM150 appears to be safe and well tolerated

- Doses between 30 and 120 mg YM150 should be considered for further development

Source: 2007 American Society of Hematology
- Cardiovascular -
RSD1235
(vernakalant)
Recommendation by Advisory Committee:

Approval
(Indication: The rapid conversion of acute atrial fibrillation to sinus rhythm)

Discussion Points*:
- Risk management (Physician Education)
- Post-marketing study
- Pharmacovigilance

FDA action date: Jan. 19, 2008

* AdComm Bulletin, Today’s Headline 12/11
YM758

- **Indications:** Atrial fibrillation, stable angina
- **Mechanism of action:**
  - Cardiac $I_f$ channel inhibition
- **Formulation:** Oral
- **Status:** Completed P-IIa trial for stable angina
- **Results:** Decided to discontinue
- **Reason:** Efficacy of YM758 has been confirmed; however, safety has not been achieved to the target profile.
- Diabetes -
YM543 / ASP1941
YM543 & ASP1941: Mechanism of Action

Excretion of excessive glucose out of the blood to the urine by inhibiting SGLT2

SGLT1: Transporter abundant mainly in the small intestine. Involved in the absorption of dietary glucose into the body. Slightly expressed in the kidney tubules as well.

SGLT2: Transporter abundant mainly in the proximal tubule of the kidney. Involved in the reabsorption of glucose filtrated in the glomeruli into the body.
**SGLT2 Inhibitor: YM543 & ASP1941**

- **Indication**: Type 2 Diabetes
- **Mechanism of action**: Stimulation of urinary glucose excretion by inhibiting SGLT2 in the kidney
- **Formulation**: Oral
- **Status**: YM543: P-IIa (Proof of concept study) in Europe
  ASP1941: P-I completed

**Target profile**
- Novel hypoglycemic agent effective in a broad spectrum of patients, irrespective of pathology (impaired insulin secretion or insulin resistance)
- No weight gain and less risk of hypoglycemia
- Can be used in combination with all kinds of hypoglycemic agents, thus suitable for combination therapy
Interim Results of YM543 / SGLT2 Inhibitor Development Plan

- POC confirmed

- interim results -

- Once daily administration of YM543 for type 2 diabetes patients in 12 weeks resulted in obvious improvement of FPG level compared to placebo

- Tendency of improvement in HbA\textsubscript{1c} level

- Confirmed clear excretion of urinary glucose

- In conclusion, POC of YM543 has been confirmed

Future development plan: Make decision at the end of POC study of YM543
- Infectious Diseases -
Telavancin
Study Summary

Objectives: To compare the efficacy and safety of telavancin to vancomycin in the treatment of hospital-acquired pneumonia (HAP) caused by Gram-positive bacteria such as methicillin-resistant Staphylococcus aureus (MRSA).

Design: Two large, multi-center, multinational, double-blind, randomized Phase 3 clinical studies (ATTAIN 1 and ATTAIN 2)

Primary endpoint / objective:
Non-inferiority in clinical cure rate
Clinical cure rate for patients infected with MRSA

Treatment:
- Telavancin: Q.D. at 10 mg/kg
- Vancomycin: B.I.D. at 1g (Dosing optimization allowed per individual site guidelines)

Enrollment: 1,503 patients in total
(464 with MRSA identified at baseline culture)
Telavancin HAP Phase3 Results

Efficacy

- Study met primary objective
  - Non-inferiority attained in AT and CE populations
- Numerically higher cure rates in MRSA pneumonia
- Numerically higher cure rates in many compromised populations
  - High APACHE scores, severe renal impairment, bacteremia and elderly
- Numerically higher ventilator-associated pneumonia (VAP) cure rates

<table>
<thead>
<tr>
<th>Population</th>
<th>Clinical cure rate (%)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Telavancin</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>All-treated (AT)</td>
<td>58.9</td>
<td>59.5</td>
</tr>
<tr>
<td>Clinically Evaluable (CE)</td>
<td>82.7</td>
<td>80.9</td>
</tr>
<tr>
<td>MRSA pneumonia</td>
<td>82.0</td>
<td>74.1</td>
</tr>
<tr>
<td>VAP</td>
<td>80.3</td>
<td>67.6</td>
</tr>
</tbody>
</table>
- Transplantation -
Drug treatment after transplant surgery

**Acute rejection**
- HSV, CMV, HBV, HCV, LISTERIA, PCP

**Infections**
- Acute rejection
- HSV, CMV, HBV, HCV, LISTERIA, PCP
- Malignancies, osteoporosis, nephrotoxicity, cardiovascular disease

**Period of most intensive immune suppression**
- Tapering of immunosuppression
- Graft failure

**Transplantation**
- 3 months

**Induction**
- Antithymocyte globulin
- Basiliximab
- Daclizumab

**Maintenance**
- Mycophenolate mofetil
- Cyclosporine
- Tacrolimus
- Sirolimus

**Unmet needs**

Source: Datamonitor, Stakeholder Opinion, P.11, Figure 2 "Organ transplantation timeline"
### Changes of treatment in transplant

<table>
<thead>
<tr>
<th>1980s</th>
<th>1990s</th>
<th>2000</th>
<th>Future</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calcineurin Inhibitor</strong>&lt;br&gt;Cyclosporine</td>
<td><strong>Calcineurin Inhibitor</strong>&lt;br&gt;Tacrolimus</td>
<td><strong>Calcineurin Inhibitor</strong>&lt;br&gt;Tacrolimus</td>
<td><strong>Tacrolimus</strong></td>
</tr>
<tr>
<td><strong>Adjunctive Agents</strong>&lt;br&gt;Azathioprine</td>
<td><strong>Adjunctive Agents</strong>&lt;br&gt;Mycophenolate Mofetil</td>
<td><strong>Adjunctive Agents</strong>&lt;br&gt;Mycophenolate Mofetil/Myfortic acid or Sirolimus/Everolimus</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td><strong>Combination therapy with these agents</strong></td>
</tr>
<tr>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td></td>
</tr>
</tbody>
</table>

**Steroids**

**Induction therapy**

- **Induction Therapy**<br>OKT3<br>ATG
- **Induction Therapy**<br>IL-2R Abs<br>Thymoglobulin
- **Induction Therapy**<br>IL-2R Abs<br>Thymoglobulin<br>Campath-1H

**Steroid use will be withdrawn**

**Induction therapy is increasing**

**NME targets relating to immunosuppression for graft rejection**

*Source: In-house*
Summary of CD40 antagonistic mAb

- **Product:** CD40 antagonistic mAb
  (a fully human anti-CD40 antagonistic monoclonal antibody)

- **Indication:** Prophylaxis of organ rejection associated with organ transplant

- **Mechanism of action and characteristics:**
  Inhibit signal transduction between T-cell and antigen-presenting cell by inhibiting interaction between CD40 and CD40L and consequently suppress cellular immune response.

  Suppress humoral immune response by inhibiting interaction between T-cell and B-cell/macrophase.

  Efficacy shown with monkey transplant model
  (Transplantation 2007;84: 1024-1028)

- **Formulation:** Injection

- **Concept:**
  Base drug which could be an alternative of calcineurin inhibitors (CNI) or
  Adjunctive drug co-administrated with CNI which could reduce the dosage of CNI
Anti-CD40 mAb: Mechanism of Action

Suppress both cellular and humoral immune response by inhibiting the binding of CD40 and CD40L between T-cell and APC

**Anti-CD40 Mab 4D11**

APC: Antigen-presenting cell
Acquisition of Agensys
- Antibody in Cancer Field-
Expected Synergy (1)

Antibody technology and know-how synergies in cancer field

- **Collection of target molecules (mostly for cancer)**
- **VelocImmune® Mice (licensed from Regeneron)**
  - Immunization
- **Screening**
  - Hybridoma generation
  - Pharmacological evaluation
  - Antibody gene isolation
  - Establishment of CHO cells
- **Not for all antibody**
  - Antibody Engineering (Fc modification)
- **Manufacture CTM**

- **Agensys Pipeline**
- **Agensys ADC technology from Seattle Genetics**
- **Agensys Tech.**
## Expected Synergy (2)

<table>
<thead>
<tr>
<th>Target discovery</th>
<th>Theme planning</th>
<th>Ab Generation</th>
<th>Evaluation</th>
<th>Ab production P0-P2a</th>
<th>P0</th>
<th>P1 P2a</th>
<th>Ab production P2b-</th>
<th>On and after P2b</th>
</tr>
</thead>
</table>

From upper stream to down stream covered by the synergies

### Current

**Agensys**
- **Cancer: Antibody Drugs**
  - **Focus of research activities:**
    - Current: H
    - Future: L

**Astellas**
- **Cancer: Small molecule drugs**
  - **Focus of research activities:**
    - Current: L
    - Future: H
- **Other therapeutic fields: Antibody Drugs**
  - **Focus of research activities:**
    - Current: M
    - Future: M

**Integration:**
- to strengthen antibody tech.
- to strengthen cancer field
**Pipeline of Agensys**

<table>
<thead>
<tr>
<th>Code No.</th>
<th>Name or Type of target</th>
<th>Cancer Indications</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGS-PSCA*</td>
<td>Prostate Stem-Cell Antigen (PSCA)</td>
<td>Prostate, Pancreatic, Bladder</td>
<td>P-1b</td>
</tr>
<tr>
<td>AGS-16M18</td>
<td>Cell Surface Enzyme</td>
<td>Kidney, Liver</td>
<td>P-0</td>
</tr>
<tr>
<td>AGS-8M4</td>
<td>Cell Surface C-type Lectin</td>
<td>Ovary</td>
<td>P-0</td>
</tr>
<tr>
<td>AGS-5ADC**</td>
<td>10 Transmembrane Transporter</td>
<td>Prostate, Lung, Breast, Ovary</td>
<td>PC</td>
</tr>
<tr>
<td>AGS-15</td>
<td>Member of Slitrk Family</td>
<td>Bladder, Lung, Breast</td>
<td>PC</td>
</tr>
<tr>
<td>AGS-34</td>
<td>Member of CAM Family</td>
<td>Melanoma, Ovary</td>
<td>PC</td>
</tr>
<tr>
<td>AGS-60</td>
<td>Member of TNF Receptor Family</td>
<td>Colon</td>
<td>PC</td>
</tr>
</tbody>
</table>

*Co-development with Merck

**Co-development with Seattle Genetics
AGS-16 is one of proprietary targets

◆ Novel cell surface enzyme
◆ Involved in tumor cell proliferation, invasion and angiogenesis
◆ Highly restricted normal tissue expression
◆ Up-regulated expression:
  Kidney cancer: clear cell >95%; papillary >80%
  Liver cancer: >40%

Clear Cell Carcinoma | Metastasis to Lymph Node | Normal Adjacent Tissue
AGS-16M18 is in the process of IND application

- Fully human IgG1 MAb with a high affinity (Kd=0.4nM)
- Inhibits target function in tumor growth, invasion and angiogenesis

Inhibition of tumor cell proliferation

![Graph showing inhibition of tumor cell proliferation](image)
AGS-16M18 Inhibits the Growth of Established Renal and Liver Carcinoma Xenografts

Patient-derived renal clear cell carcinoma

Hepatocellular carcinoma

AGS-16M18 inhibited tumor growth by 61% (P<0.01)

AGS-16M18 inhibited tumor growth by 82% (P<0.0003)