Manuseio da Imunossupressão no Pós-Operatório Tardio

Guideline

Definição:
any document that aims to streamline
particular processes according to a set routine.

Additional objectives of clinical guidelines are to standardize medical care, to raise quality of care, to reduce several kinds of risk (to the patient, to the healthcare provider, to medical insurers and health plans) and to achieve the best balance between cost and medical parameters such as effectiveness, specificity, sensitivity, resolutiveness, etc. It has been demonstrated repeatedly that the use of guidelines by healthcare providers such as hospitals is an effective way of achieving the objectives listed above, although they are not the only ones

IMUNOSSUPRESSÃO

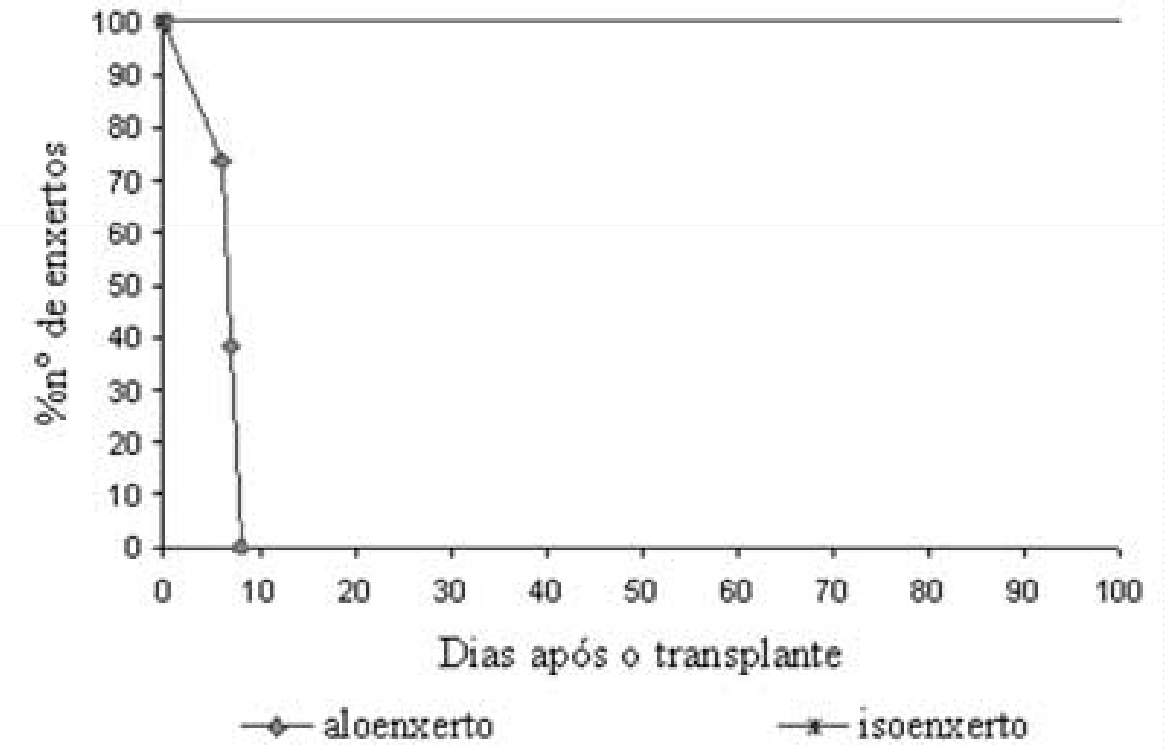
- Fase inicial
  - Mais drogas
  - Doses maiores
  - Efeitos colaterais dose-dependentes

  - Complicações técnicas
  - Infecções

  - Curva de sobrevida

IMUNOSSUPRESSÃO

- Curva de sobrevida



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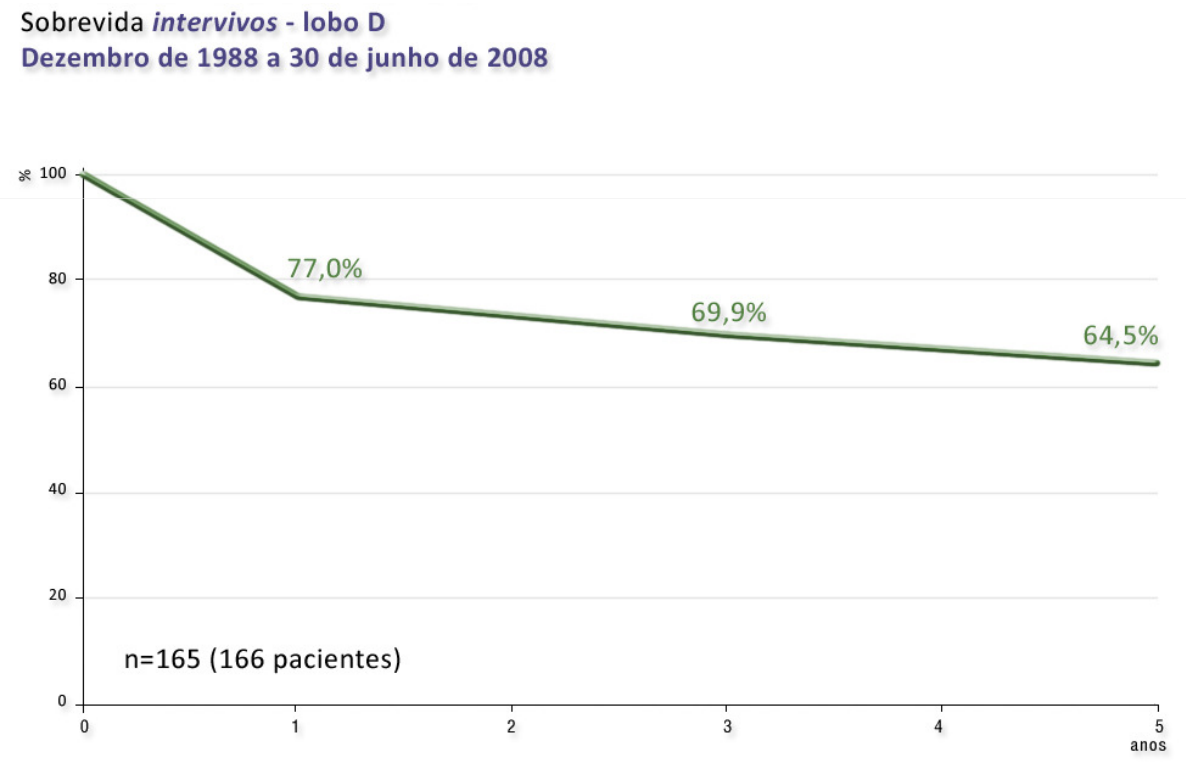
- Curva de sobrevida



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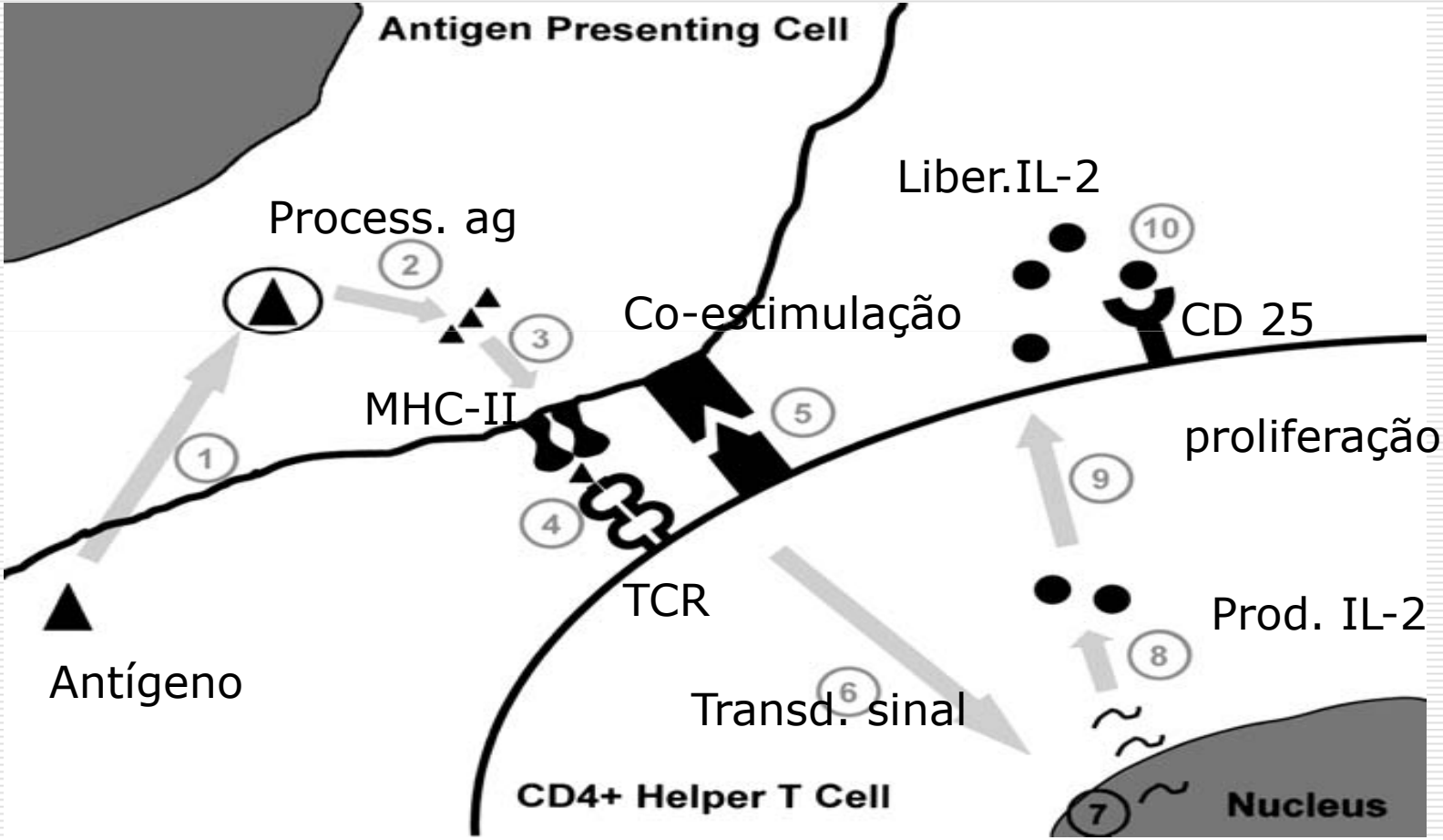

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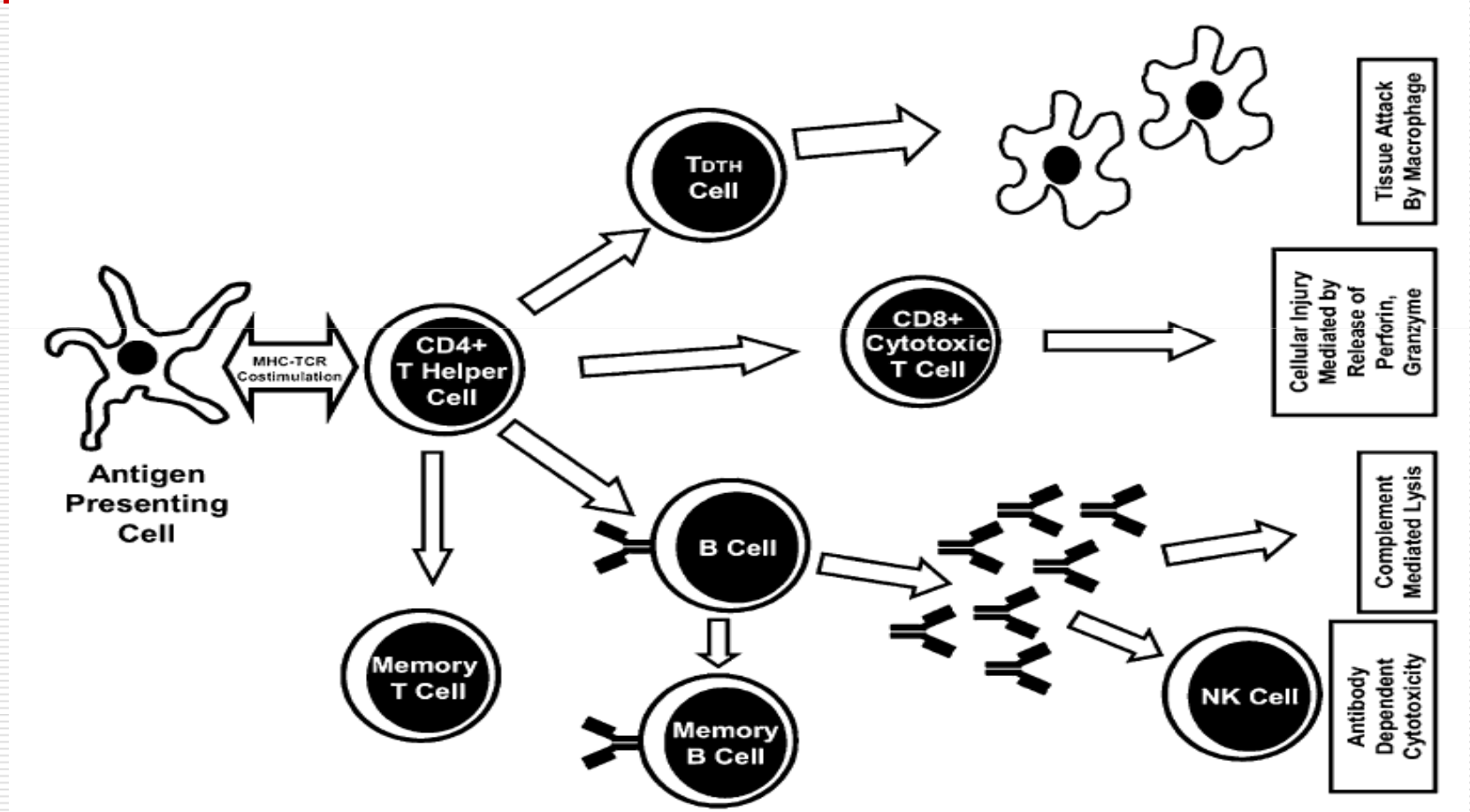

IMUNOSSUPRESSÃO

- Fase inicial
  - Drogas utilizadas para indução
    - Anticorpos
      - ATGAM – glob anti-timocítica – cavalo
      - rATG – glob anti-timocítica – coelho
      - Muromonab-CD3 = OKT3 – camundongo
      - Daclizumab – Zenapax (anti-receptor de IL-2)
      - Basiliximab – Simulect (anti-receptor de IL-2)
      - Alemtuzumab – Campath-1H (anti-CD52)

IMUNOSSUPRESSÃO

- Fase de manutenção
  - Drogas utilizadas
    - Corticosteróides
    - Inibidores de calcineurina
    - Antiproliferativas
    - Inibidoras da m-TOR
- Perspectivas
    - Indução de tolerância
    - Novas drogas

IMUNOSSUPRESSÃO

Major adverse effects of immunosuppressive agents

Corticosteroids	Calcineurin inhibitors	Mycophenolate mofetil	Sirolimus	Azathioprine	OKT3	Daclizumab/ basiliximab	Antithymocyte globulin
Diabetes mellitus	Anemia	Bone marrow suppression	BOOP (bronchiolitis obliterans organizing pneumonia)	Alopecia	Aseptic meningitis	Hypersensitivity reaction	Hypersensitivity reaction
Gastrointestinal toxicity	Diabetes mellitus	Anemia	Fever	Bone marrow suppression	Diarrhea		Serious infections
Colon perforation	Electrolyte imbalance	Neutropenia	Headache	Leukopenia	Expressive aphasia		T-cell depletion
Gastric ulcer	Hyperkalemia	Thrombo-cytopenia	Hepatic artery thrombosis	Macrocytic anemia	Hypersensitivity reaction		Leukopenia
Pancreatitis	Hypomagnesemia	Gastrointestinal toxicity	Hyperlipidemia	Pancytopenia			Thrombo-cytopenia
Growth retardation	Gastrointestinal toxicity	Abdominal pain	Infections	Thrombocytopenia			
Hypertension	Diarrhea	Diarrhea	Interstitial pneumonitis	Gastrointestinal toxicity			
Infections	Nausea	Vomiting	Nausea	Nausea/vomiting			
Muscular	Hearing deficit	Infections	Oral ulcers	Anorexia			
Myalgia	Hemolytic-uremic syndrome		Pleural effusion	Diarrhea			
Myositis	Hyperlipidemia			Oral ulcers			
Neuropsychiatric	Hypertension			Esophagitis			
Depression	Infections			Steatorrhea			
Euphoria	Nephrotoxicity			Pancreatitis			
Insomnia	Neurotoxicity			Hepatic toxicity			
Osteodystrophy	Akinetic mutism			Hepatitis			
Avascular necrosis	Convulsions			Cholestasis			
Osteopenia	Headache			Veno-occlusive disease			
Osteoporosis	Insomnia			Hypersensitivity reaction			
Poor wound healing	Peripheral neuropathy						
	Tremors						
	Cyclosporine:						
	Gingival hyperplasia						
	Hirsutism						

IMUNOSSUPRESSÃO

- Fase tardia (*long-term*)
  - Doses menores
  - Efeitos colaterais "cumulativos"
  - Toxicidade "crônica"

  - Doença de base
  - Doenças concomitantes

"*Long-term*" - manutenção

- Drogas
  - Corticosteróides
    - Depleção de linfócitos
    - Diabetes
    - Hiperlipemia
    - Hipertrofia gengival

"*Long-term*" - manutenção

- Drogas
  - Corticosteróides
    - Diabetes
      - Redução da produção e liberação de insulina
      - Aumento da resist. periférica à insulina
      - Neoglicogênese hepática, degradação de proteína muscular, lipólise

"*Long-term*" - manutenção

- Drogas
  - Corticosteróides
    - Hiperlipemia
      - Ação em várias enzimas (>acetil CoA carboxilase, ácido graxo sintetase e HMG CoA reductase, < lipase lipoproteica)
      - > VLDL, colesterol total e triglicérides, <HDL

"*Long-term*" - manutenção

- Drogas
  - Inibidores de calcineurina (ligam-se às imunofilinas e inibem a síntese de IL-2 por bloqueio da transcrição do DNA)
  - Ciclosporina e tacrolimo
    - Diabetes
    - Hiperlipemia
    - Hipertensão arterial
    - Nefrotoxicidade
    - Neurotoxicidade

Ciclosporina e tacrolimo

- Monitoramento dos níveis sanguíneos
- Nível tóxico ~ terapêutico
- CYP450

Citocromo P4503A

- Responsável pelo metabolismo de:
  - Maioria dos bloqueadores de canais de cálcio
  - Maioria dos benzodiazepínicos
  - Maioria dos inibidores de protease do HIV
  - Maioria das estatinas
  - Ciclosporina, tacrolimo
  - Maioria dos anti-histamínicos não sedativos
  - Presente no TGI e fígado

Inibidores de CYP3A

- Cetoconazole
- Fluconazole
- Itraconazole
- Cimetidina
- Claritromicina
- Eritromicina
- Suco de toronja

Indutores de CYP3A

- Carbamazepina
- Rifampicina
- Rifabutina
- Ritonavir
- *Hypericum perforatum*


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Programa Internacional de Monitoramento - OMS
Farmacovigilância
Alertas Federais de Farmacovigilância
Brasília, 15 de março de 2002
Erva de São João - (Hypericum perforatum) - Fiscalização intensificada através da Resolução - RE nº 357 , de 28 de fevereiro de 2002
Alerta SNVS/Anvisa/Ufarm nº 7, de 15 de março de 2002
A Erva de São João (Hypericum perforatum) é um fitoterápico utilizado popularmente como sedativo leve, colagogo, para tratamento de inflamações crônicas do estômago, do fígado, da vesícula, dos rins e afecções ginecológicas. Também é empregada pela população para tratamento da ansiedade, tensão nervosa, perturbações na menopausa e síndrome pré -menstrual, apesar de todas estas supostas indicações não terem sido comprovadas cientificamente até o momento. Por este motivo, a única indicação aprovada pela Anvisa, respaldada por evidências clínicas, é para tratamento de depressão leve e moderada.
Recentes relatos de agências regulatórias de produtos pelo mundo indicam importantes interações entre os produtos à base da Erva de São João (Hypericum perforatum) e medicamentos prescritos, tais como: ciclosporina, digoxina, contraceptivos orais, teofilina, varfarina, indinavir e potencialmente com diversos outros medicamentos vendidos sob

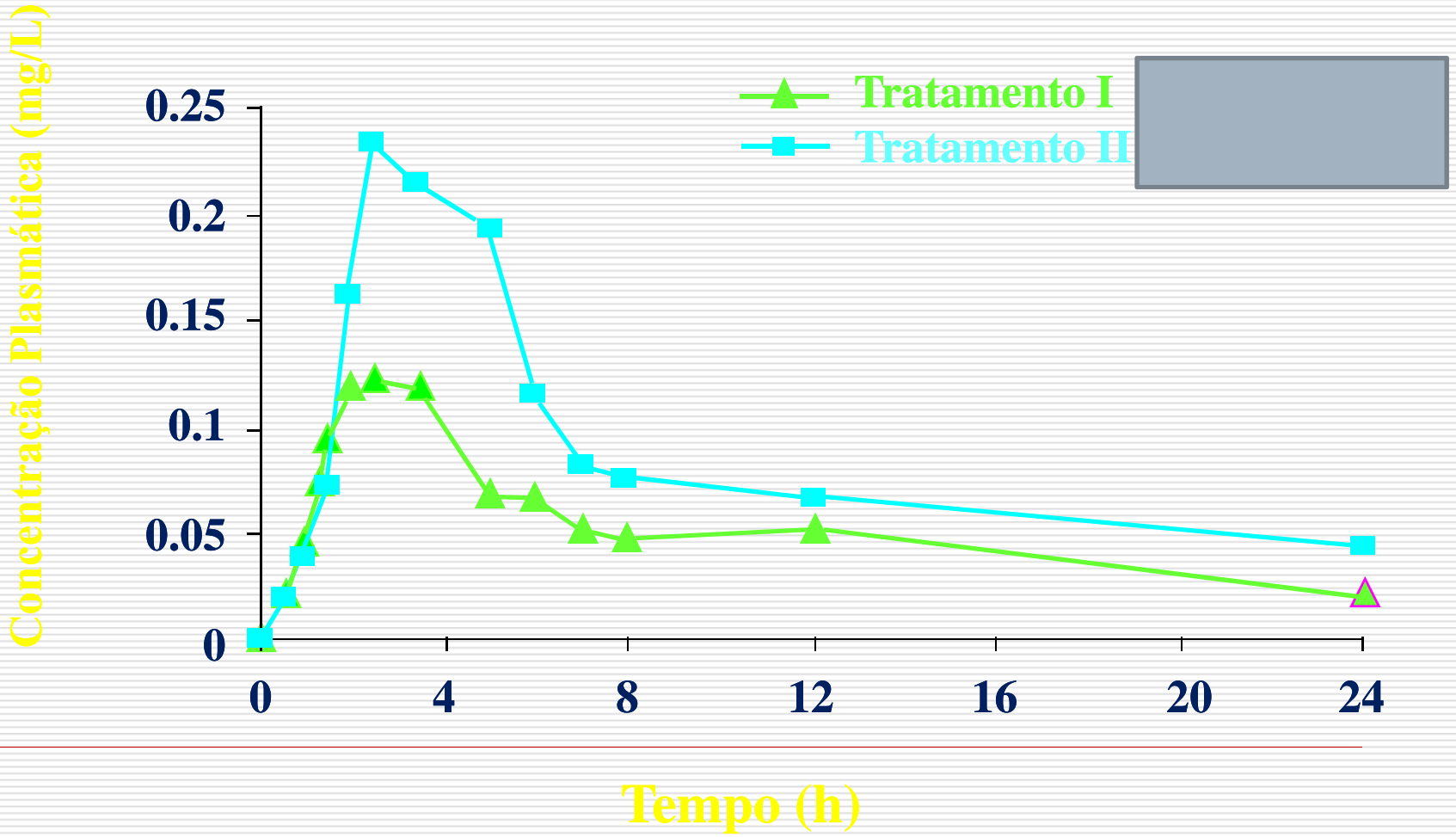
Tabela 1 – Importantes Interações com *Hypericum perforatum*

DROGA	EFEITOS DA INTERAÇAO HYPERICUM + DROGA
Indinavir	Redução dos níveis sanguíneos da droga com possível perda da supressão do HIV
Varfarina	Redução do efeito anticoagulante da droga e necessidade de aumento da dose de Varfarina
Ciclosporina	Redução dos níveis sanguíneos da droga com risco de rejeição do transplante
Contraceptivos orais	Redução dos níveis sanguíneos da droga com risco de gravidez não intencional
Anticonvulsivantes (Carbamazepina; Fenobarbital; Fenitoína	Redução dos níveis sanguíneos da droga com risco de ataques convulsivos
Digoxina	Redução dos níveis sanguíneos da droga com risco para a perda do controle do ritmo cardíaco
Teofilina	Redução dos níveis sanguíneos da droga com perda do controle da asma

*Fonte:http://www.mca.gov.uk/ourwork/monitorsafequalmed/currentproblems/cpmay2000.pdf

Os consumidores brasileiros podem estar adquirindo produtos a base de Erva de João (**Hypericum perforatum**) sem nenhuma avaliação médica, a partir de aquis

Administração de itraconazol (100 mg) em voluntários sadios



Ciclosporina e tacrolimo

- Prós e contras
  - Ciclosporina
    - Mais nefrotóxica
    - Mais "hipertensiva"
    - Mais dislipidêmica
    - Hipertrofia gengival/hirsutismo
  - Tacrolimo
    - Mais diabetogênico
    - Mais neurotóxico
    - Mais alopecia, hipercalemia, hipomagnesemia

"*Long-term*" - manutenção

- Drogas
  - Antiproliferativos
    - Azatioprina
      - Inibidores de síntese de purinas
      - Alopurinol = inibição metabolismo da AZA
    - Micofenolato
      - MMF: especificidade para LT e LB
      - MMF-> Ac micofenólico -> MPAG -> MPA
      - Albumina/MPAG e MPA
      - Disfunção renal: acumula MPAG

"*Long-term*" - manutenção

- Drogas
  - Antiproliferativos
    - Micofenolato de sódio
      - Efeitos colaterais sistema digestivo
      - Menor biodisponibilidade com CyA:
        - inibição do ciclo entero-hepático por redução da excreção biliar de MPAG
        - Tacrolimo inibe enzima que metaboliza MPA para MPAG
      - Outras drogas: metronidazol, norfloxacino reduzem flora intestinal

"*Long-term*" - manutenção

- Drogas
  - Inibidores de m-TOR (mammalian target of rapamycin)
    - Sirolimo (rapamicina), everolimo
      - Inibe sinal para proliferação
      - Indução/PO recente: TAH, deiscência de anastomose de via aérea
      - Pneumonite, pode ser fatal
      - + CyA= aumenta risco microangiopatia hemorrágica em Tx renal (e +pâncreas)

"*Long-term*" - manutenção

- Drogas
  - Inibidores de m-TOR
    - Sirolimo
      - P450 3A:
        - CyA: menores doses
        - Interações medicamentosas
      - 1x/dia
      - Dosagem sérica ≥semanal
      - Dislipidemias severas
      - Úlcera oral

"*Long-term*" - manutenção

- Drogas
  - Novidades!

FK778, a novel compound with multiple modes of action - a breakthrough in transplant immunosuppression?

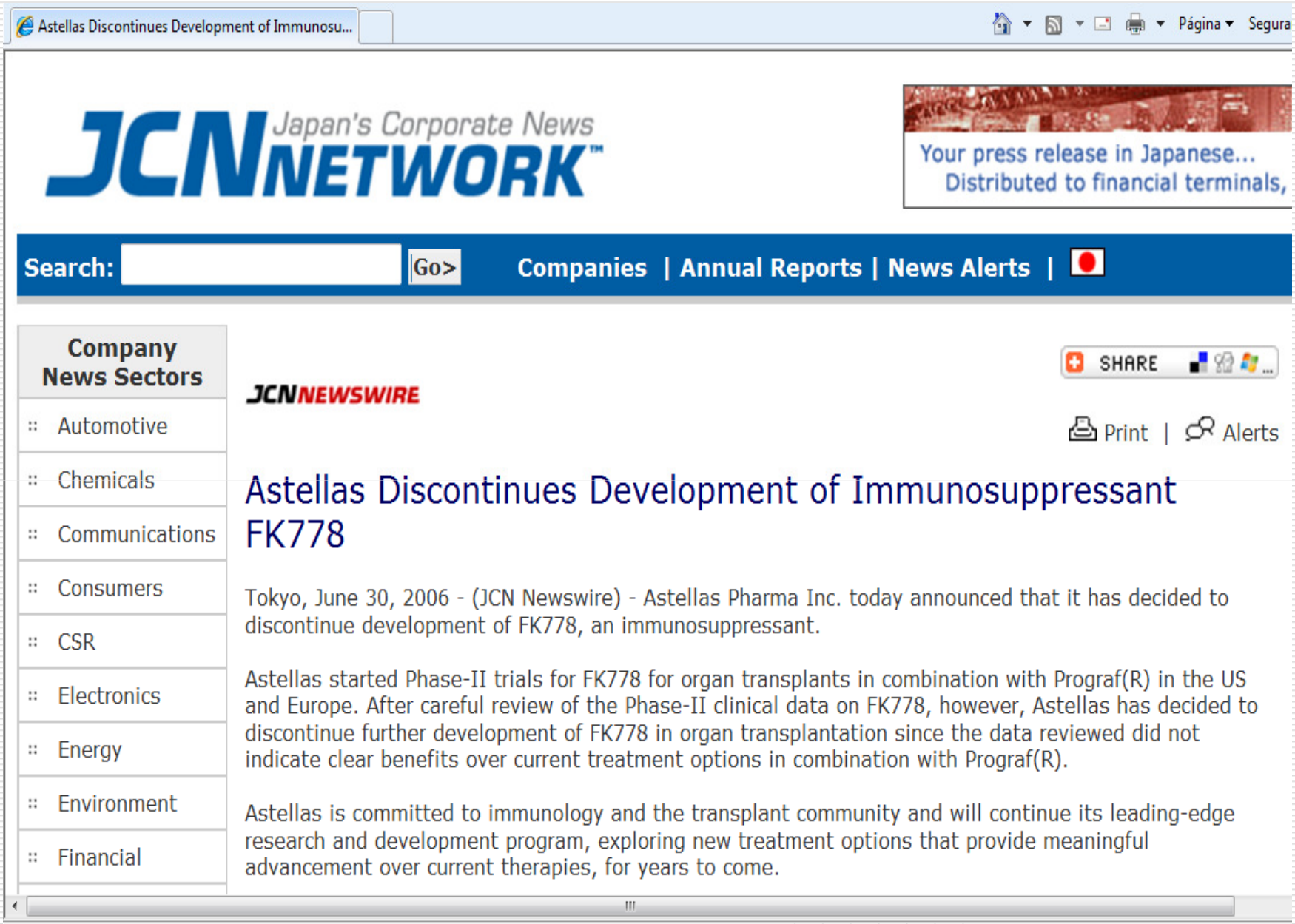
Venice, Italy, September 23 /PRNewswire/ -- First clinical data presented today at the 11th Congress of the European Society for Organ Transplantation in Venice suggest FK778, a novel compound with multiple mechanisms of action, is efficacious, well tolerated and safe in kidney transplant patients, potentially offering a breakthrough in immunosuppressive therapy.

FK778 is the first of a new class of low molecular weight immunosuppressants, the malononitrilamides, currently under development for organ transplantation. In animal models, FK778 has been shown to block both cellular (T cell) and humoral (antibody) immune responses, potentially allowing FK778 to prevent not only acute rejection but also chronic allograft dysfunction - notoriously difficult to treat and one of the main reasons for late graft loss.

Final results of the Phase II study (1)(n=149 adult renal transplant recipients) revealed that after 4 months treatment FK778 was efficacious and well tolerated when used in combination with the calcineurin inhibitor Prograf(r) (tacrolimus) and corticosteroids. Presenting the results on behalf of the study group, Professor Yves Vanrenterghem (Department of Nephrology, Universitaire Ziekenhuizen, Leuven, Belgium) revealed that FK778 treated patients showed lower acute rejection rates, especially when patients were under higher drug exposure early on after transplantation.

Unlike currently available immunosuppressants, FK778 exerts its immunosuppressive activity at the molecular level via the suppression of de-novo pyrimidine biosynthesis, inhibiting the action of dihydroorotate dehydrogenase, an enzyme critical in the process, and consequently inhibiting cell proliferation.

In addition to its immunosuppressive properties, FK778 has also been shown in in-vitro and animal studies to exhibit antiviral activity, inhibiting the virion assembly process of cytomegalovirus (CMV) and polyoma virus. This is important in immunocompromised transplant patients because CMV infection is a common complication after transplantation and for patients affected it is a risk factor for chronic allograft dysfunction. For polyoma virus the effect of FK778 is even more important, because the infection often causes subsequent graft failure


Astellas Discontinues Development of Immunosu...
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Astellas Discontinues Development of Immunosuppressant FK778
Tokyo, June 30, 2006 - (JCN Newswire) - Astellas Pharma Inc. today announced that it has decided to discontinue development of FK778, an immunosuppressant.
Astellas started Phase-II trials for FK778 for organ transplants in combination with Prograf(R) in the US and Europe. After careful review of the Phase-II clinical data on FK778, however, Astellas has decided to discontinue further development of FK778 in organ transplantation since the data reviewed did not indicate clear benefits over current treatment options in combination with Prograf(R).
Astellas is committed to immunology and the transplant community and will continue its leading-edge research and development program, exploring new treatment options that provide meaningful advancement over current therapies, for years to come.

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Promising new drug to stop kidney transplant rejection

Main Category: Cholesterol
Article Date: 18 May 2004 - 0:00 PDT

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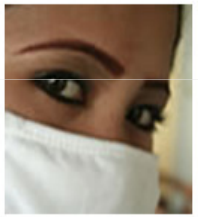
Clinical trial shows drug may offer a new option to prevent rejection of transplanted kidneys.

Results of a preliminary study suggest that a treatment called LEA29Y works as well as the standard therapy, cyclosporine, to prevent acute kidney transplant rejection, with less potential for long-term harm to the organ and the patient, and better functioning of the transplanted kidney.



Swine Flu Updates

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The Immune System's Role In Bone Loss Uncovered By UCLA Scientists
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Headline **Which of 2009's launches will be future blockbusters?**

Source EP Vantage

Company Amgen

Related: Eli Lilly, GlaxoSmithKline, InterMune, Johnson & Johnson, Roche, Takeda

Date February 17, 2009

A look at this year's biggest product launches, in terms of future sales potential, reveals that unsurprisingly biotechnology will be the source of 2009's most valuable new drugs, with Amgen's denosumab topping the table.

The following tables detail the 10 biggest biotech and 10 biggest conventional drugs that financial analysts expect to reach the market this year, ranked on 2014 consensus forecasts, provided by EvaluatePharma. With six predicted to reach blockbuster status six years after launch, their progress or otherwise in front of regulators will be of great interest this year.

However, it should be remembered that nowadays regulatory delays are commonplace, and it is likely a significant proportion of the drugs identified will not make it to market before the end of the year. EP Vantage conducted the same analysis 12 months ago, and followed up 2008's cohort of most valuable launches earlier this month, finding that only 7 out of that year's 20 reached the market as expected (*Failure to launch for last year's big hopes, February 6, 2009*).

That represents a 70% failure rate, something that does not seem to be taken into account by many analysts, who continue to optimistically factor in hitch-free approval processes.

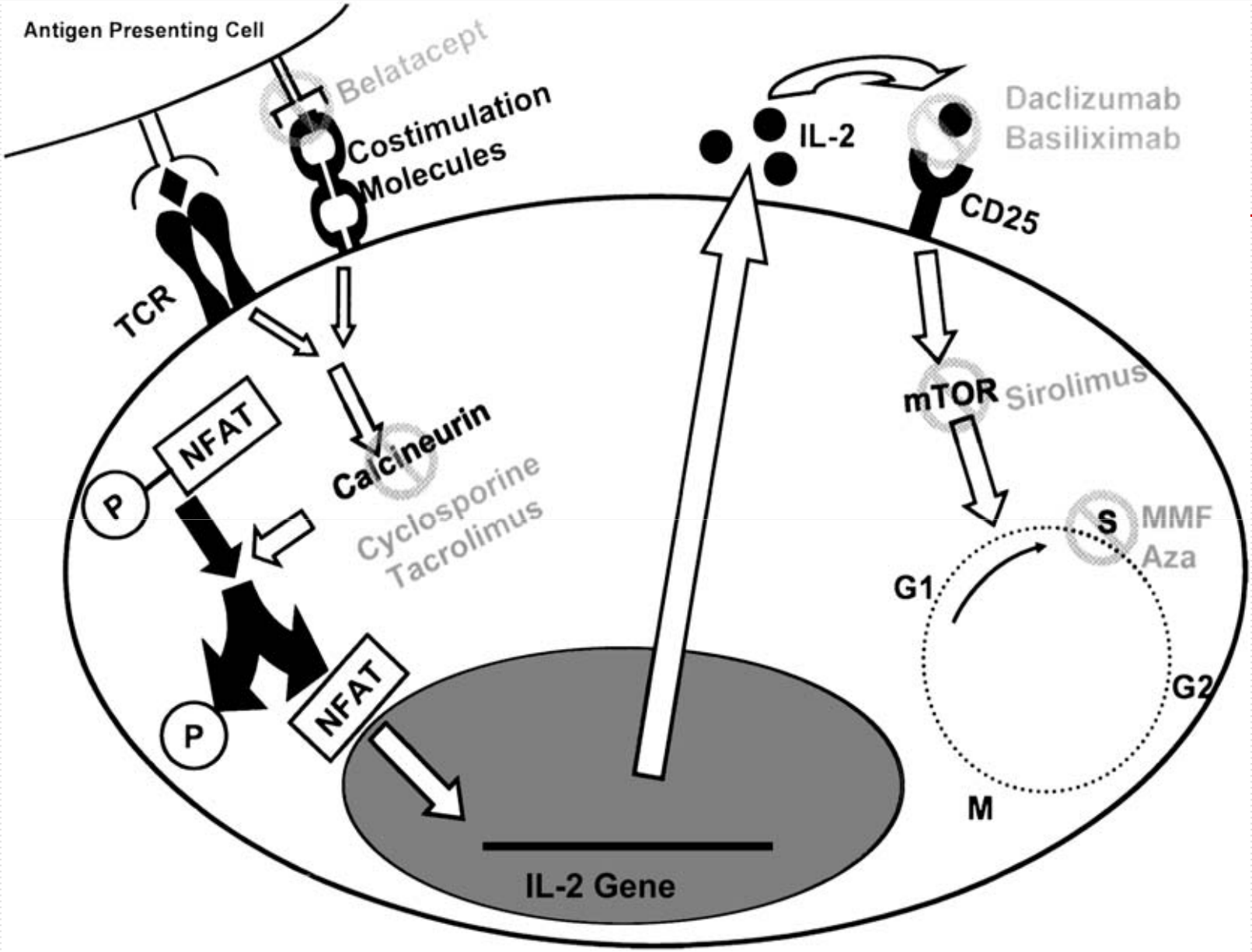
Last year's hangovers

Still, some big approvals are already in the bag for 2009: Actemra, Takeda's Kapidex in the US and Glaxo's Synflorix, which has been recommended for approval in Europe.

Whether this year will hold any spectacular failures remains to be seen. Last year's knock back for Merck & Co's Cordaptive robbed 2009 of one of its biggest launches. With phase III data still not available for a handful of the top biotech candidates, such as Abbott Laboratories' psoriasis treatment ABT-874 or Bristol-Myers Squibb's organ transplantation drug LEA29Y, there is still plenty of time for the rankings to shift.

However, with biotech accounting for four of the top five biggest launches anticipated this year, what is certain is that the area will continue to attract a large proportion of the industry's R&D dollars.

The biggest launches of 2009?							Annual Sales WW ($m)	
	Rank	Product	Generic Name	Therapeutic Subcategory	Company	Phase (Current)	2009	2014
Biotechnology	1	Denosumab (AMG 162)	denosumab	Bone calcium regulators	Amgen	Filed	47	3,737
	2	Simponi	golimumab	Other anti-rheumatics	Johnson & Johnson/Schering-Plough	Filed	165	2,529
	3	Actemra	tocilizumab	Other anti-rheumatics	Roche	Approved	233	2,255
	4	Victoza	liraglutide	Anti-diabetics	Novo Nordisk	Filed	152	1,772
	5	Numax	motavizumab	Anti-virals	AstraZeneca	Filed	449	993
	6	Arzerra	ofatumumab	Anti-neoplastic MAbs	GlaxoSmithKline	Filed	17	620
	7	ABT-874	-	Immunosuppressants	Abbott Laboratories	Phase III	30	578
	8	LEA29Y	belatacept	Immunosuppressants	Bristol-Myers Squibb	Phase III	11	565


Antigen Presenting Cell
Belatacept
Costimulation Molecules
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IL-2
Daclizumab
Basiliximab
CD25
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Sirolimus
NFAT
Calcineurin
Cyclosporine
Tacrolimus
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MMF
Aza
G1
G2
M
NFAT
P
IL-2 Gene

IMUNOSSUPRESSÃO
no pós-op tardio

- Paciente
  - Idade, sexo, história familiar
- Drogas
  - Toxicidades múltiplas
  - Interações medicamentosas
- Novidades
  - Ótimas, com cautela.