COMPLEX ALLERGIES IN THE XXI CENTURY

Cancer patients:
1. survive longer
2. are exposed to multiple chemotherapy treatments:
3. outcomes of clinical trials indicate that first line therapy prolongs life

Increase in Atopic diseases: more than 20% of the general population is allergic to environmental and/or food allergens
METHOTREXATE HYPERSENSITIVITY

18 yo healthy female accomplished athlete presents after a lacrosse match chest pain, SOB, treated for few weeks with NSAIDS, nebulizers
CT : Large mediastinal mass
PM B cell lymphoma FAB/LMB96: high grade , aggressive disease
Day 1 : Intrathecal Methotrexate
Day 8 : IV Methotrexate
    Reaction: 20 min into the infusion SOB, wheezing O2 sat 80% ,
            BP 90/40 , flushed

Anaphylaxis !!!!
METHOTREXATE HYPERSENSITIVITY

Infusion stopped, treated with steroids, anti-H1, anti-H2, no epi
Immediate recovery

Next day: pre-medicated with increased steroids 200 mg solumedrol
anti-histamines H1 and H2
Reactions: Within 5 min of the start SOB, O2 sat 80%, BP 70/30,
generalized flushing, desorientation and syncope

Code called, infusion stopped, epi given and Methotrexate discontinued
METHOTREXATE HYPERSENSITIVITY
ANAPHYLACTIC NON-IGE

Tryptase:  50 ng/ml within one hour of the reaction (NI 11ng/ml),
4 ng/ml baseline (4 weeks later)

Skin Test: no available

Diseases progression of methotrexate

Oncology wants first line therapy: only chance to induce remission

Evaluation by allergy:
- anaphylaxis Grade 3
- candidate for rapid desensitization
- risk: high for repeat anaphylaxis
SYMPTOMS OF HYPERSENSITIVITY

Carboplatin
Paclitaxel
Doxorubicin/Adriamycin
Rituximab

Chemotherapeutic Agents

Cutaneous
Cardiovascular
Respiratory
Throat Tightness
Gastrointestinal
Neurological/Muscular

Castells et al JACI 2008
HYPERSENSITIVITY REACTION TO CARBOPLATIN
ANAPHYLACTIC IGE

49 year old female with ovarian cancer
Treated with Taxol and carboplatin x 6 cycles with no side effects
Recurrence of cancer, restarted on Taxol and Carboplatin for 6 more cycles
2\textsuperscript{nd} infusion with Carboplatin (8 cycle): cramping, abdominal pain, flushing/pruritus, diffuse urticarial rash, SOB, hypotension, code
Skin test to carboplatin : positive
INCIDENCE OF CARBOPLATIN HYPERSENSITIVITY

patients receiving > 7 cycles of carboplatin have 27% of HSR, and 50% of those patients develop moderate to severe symptoms (anaphylaxis).

Increased pre-medication (steroids) and re-infusion does not prevent HSR reactions.

Cross-reactivity among platins is high (carboplatin>cisplatin>oxaliplatin).
# SKIN TESTING

**CASTELLS ET AL (2013 MANUSCRIPT IN PREPARATION)**

<table>
<thead>
<tr>
<th>(mg/ml)</th>
<th>Prick</th>
<th>Intradermal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10/5 (irritant)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>0.01</td>
<td>0.001</td>
</tr>
<tr>
<td>Rituximab</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
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</table>
Negative Predictive Value of Skin Testing
Hesterberg et al JACI 2009

<table>
<thead>
<tr>
<th>ST</th>
<th>&lt;6 mo</th>
<th>&gt;6 mo</th>
<th>Total</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Positive</td>
<td>20</td>
<td>5</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>4</td>
<td>9</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>14</td>
<td>38</td>
<td>&lt;0.01</td>
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<tr>
<td>% Positive</td>
<td>83</td>
<td>36</td>
<td>66</td>
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</tr>
</tbody>
</table>
Anaphylaxis
Hypersensitivity IgE/non-IgE

IgE Anaphylaxis refers to a systemic, immediate hypersensitivity reaction due to the IgE-mediated release of mediators from mast cells and/or basophils (positive skin test and serum specific IgE)

Non-IgE Anaphylactic event refers to a clinically similar event in which IgE cannot be identified or mast cells/basophils are activated by other mechanisms (elevated TRYPTASE)

Clinically the symptoms and the treatment are the same: EPINEPHRINE

MAST CELL HETEROGENEITY

TRYPTASE/CHYMASE/CPA

TRYPTASE

Skin, Submucosal and Connective Tissues
Histamine
Proteoglycans
Prostaglandins, Leukotrienes

Alveoli, Mucosal Tissues
Histamine
Prostaglandins, Leukotrienes

Skin, Submucosal and Connective Tissues
Histamine, Proteoglycans
Prostaglandins, Leukotrienes
MEDIATORS RELEASED FROM ACTIVATED MAST CELLS

LIPID MEDIATORS
- PGD$_2$
- LTB$_4$
- LTC$_4$

CYTOKINES (31)
- TNF-α
- GM-CSF
- IL-1β
- IL-3
- IL-6
- IL-10

PREFORMED MEDIATORS
- Serine Proteases
- Proteoglycans
- Histamine
- Carboxypeptidase A
DRUG DESENSITIZATION
EVOLVING CONCEPTS

Requires the introduction of a potentially lethal medication to a highly sensitized patient: High risk procedure:
Performed in critically ill patients: survival depends on administration of a medication to which a patient has a previous history of a severe adverse reaction
No alternative medications are available or the alternatives (second and third line choices) have less demonstrated therapeutic value than first line treatment
CURRENT UNDERSTANDING

Re introduction of a medication inducing a hypersensitivity reaction
Achieved by increasing doubling non-activating doses
It is a temporary phenomenon
Antigen specific
Can be maintained by continuous administration
Re-desensitization is needed if 2 half lives of the medication have spanned
Can only be done by trained allergists
CELLULAR TARGETS

- **Mast cells:**
  - positive skin test
  - negative after desensitization

- **Side effects:**
  - 10-30% of patients
  - consistent with mast cell/basophil mediators release
**Effect of desensitization on skin test reactivity**

Table 4.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Histamine (prick)</td>
<td>Diluent (intradermal)</td>
</tr>
<tr>
<td>Before desensitization</td>
<td>positive (5/15)</td>
<td>negative (4/0)</td>
</tr>
<tr>
<td>After desensitization</td>
<td>positive (4/13)</td>
<td>negative (4/0)</td>
</tr>
</tbody>
</table>

*Wheal produced by carboplatin (intradermal) versus wheal produced by histamine (prick).*
Mechanisms of rapid desensitizations

Tyrosine Phosphorylation/Activation of Lyn, Syk, PLC-γ

SHP-1

Mast Cell activation

Castells et al. Nature Immunology 2001
Goldstein 2002,
Kepley 2005
Rapid desensitization blocks the release of pre-formed mediators

Sancho et al EJI 2011
Rapid desensitization blocks the metabolism of AA acid and production of Prostaglandins and Leukotrienes

Sancho et al EJI 2011
Desensitization impairs calcium influx and is specific
Sancho et al EJI 2011

Cells desensitized to one antigen (DNP) respond to a challenge with a second antigen (OVA)
DESENSITIZATION IMPAIRS ACUTE AND LATE PHASE REACTIONS AND PRODUCTION OF CYTOKINES TNF-α AND IL6

SANCHO ET AL EJI 2011
DURATION OF RAPID DESENSITIZATION

As long as the desensitizing antigen is present mast cells remain desensitized.

Sancho et al EJI 2011
ANTIGEN/IGE/FCERI COMPLEX IS NOT INTERNALIZED DURING RAPID DESENSITIZATION

SANCHO ET AL. EJI 2011
ANTIGEN/IGE/FCERI COMPLEX INTERNALIZATION IS SPECIFIC AND DOES NOT PREVENT ACTIVATION THROUGH NON-DESENSITIZED ANTIGENS

SANCHO ET AL. EJI 2011
CANDIDATES FOR RAPID DESENSITIZATION

No age limitations
Informed consent
Type I hypersensitivity reaction (anaphylaxis IgE/non IgE)
Positive skin test

**Exclusion criteria:**
Type III or Type IV reactions
Steven’s Johnson Syndrome
Toxic Epidermal Necrolysis
ACE-induced angioedema
RISK STRATIFICATION

Low Risk
- FEV1 > 1.5 L
- No cardiac history
- Mild reaction: Grade 1: skin limited
  Grade 2: 2 organ/systems

High Risk: MICU
- FEV1 < 1.5 L
- Cardiac Disease w/wo beta blockade
- Severe reaction: Grade 3
  Loss of consciousness
  Intubation
METHOTREXATE 12 STEP DESENSITIZATION PROTOCOL

Table 1. Methotrexate 12-step desensitization protocol.

A. Infusion protocol.

<table>
<thead>
<tr>
<th>Step</th>
<th>Concentration (mg/ml)</th>
<th>Rate (ml/h)</th>
<th>Time (min)</th>
<th>Volume infused per step (ml)</th>
<th>Administered dose (mg)</th>
<th>Cumulative dose (mg)</th>
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<tbody>
<tr>
<td>1</td>
<td>0.678</td>
<td>2</td>
<td>15</td>
<td>0.50</td>
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<td>15</td>
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<td>0.678</td>
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<tr>
<td>5</td>
<td>6.784</td>
<td>5</td>
<td>15</td>
<td>1.25</td>
<td>8.48</td>
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<td>6</td>
<td>6.784</td>
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<td>15</td>
<td>2.5</td>
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<td>9</td>
<td>67.31</td>
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<td>638</td>
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<td>11</td>
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<td>15</td>
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<td>174</td>
<td>232.5</td>
<td>15,648.7</td>
<td>16,960</td>
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</table>

B. Premedications
REACTION DURING METHOTREXATE DESENSITIZATION

At step 12 palmar pruritus, flushing, cough, slight SOB, BP 100/60

Infusion stopped

Medications: aspirin, singulair, methylprednisolone, diphenhydramine, pepcid

Infusion restarted and finished
**METHOTREXATE DESENSITIZATION PROTOCOL MODIFIED 16 STEP PROTOCOL**

Table 2. Methotrexate 16-step desensitization protocol.

A. Infusion protocol

<table>
<thead>
<tr>
<th>Step</th>
<th>Concentration</th>
<th>Rate (ml/hr)</th>
<th>Time (min)</th>
<th>Volume infused (ml)</th>
<th>Dose administered (mg)</th>
<th>Cumulative dose (mg)</th>
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<tr>
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<td>0.034 mg/ml</td>
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<td>0.625</td>
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<td>0.034 mg/ml</td>
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<td>1.25</td>
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<td>0.15</td>
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<td>4</td>
<td>0.034 mg/ml</td>
<td>20</td>
<td>15</td>
<td>5</td>
<td>0.168</td>
<td>0.32</td>
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<tr>
<td>5</td>
<td>0.672 mg/ml</td>
<td>2.5</td>
<td>15</td>
<td>0.625</td>
<td>0.42</td>
<td>0.74</td>
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<tr>
<td>6</td>
<td>0.672 mg/ml</td>
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<td>15</td>
<td>1.25</td>
<td>0.84</td>
<td>1.6</td>
</tr>
<tr>
<td>7</td>
<td>0.672 mg/ml</td>
<td>10</td>
<td>15</td>
<td>2.5</td>
<td>1.7</td>
<td>3.3</td>
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<tr>
<td>8</td>
<td>0.672 mg/ml</td>
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<td>15</td>
<td>5</td>
<td>3.4</td>
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<tr>
<td>9</td>
<td>6.72 mg/ml</td>
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<td>15</td>
<td>1.25</td>
<td>8.4</td>
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<td>10</td>
<td>6.72 mg/ml</td>
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<td>15</td>
<td>2.5</td>
<td>16.8</td>
<td>31.8</td>
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<tr>
<td>11</td>
<td>6.72 mg/ml</td>
<td>20</td>
<td>15</td>
<td>5</td>
<td>33.6</td>
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<td>14</td>
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<td>633</td>
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<td>10</td>
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<tr>
<td>16</td>
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<td>232.5</td>
<td>232.5</td>
<td>15501</td>
<td>16800</td>
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B. Premedications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Route</th>
<th>Timing</th>
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<tr>
<td>Cetirizine</td>
<td>10 mg</td>
<td>PO</td>
<td>13 and 1 hour(s) before the infusion, then daily for 5 days</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>50 mg</td>
<td>IV or PO</td>
<td>1 hour before start of infusion</td>
</tr>
<tr>
<td>Methylprednisone</td>
<td>63 mg</td>
<td>IV</td>
<td>1 hour before start of infusion</td>
</tr>
<tr>
<td>Montelukast</td>
<td>10 mg</td>
<td>PO</td>
<td>13 and 1 hour(s) before start of infusion</td>
</tr>
<tr>
<td>Prednisone</td>
<td>50 mg</td>
<td>PO</td>
<td>13 and 7 hours before start of infusion</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>150 mg</td>
<td>PO</td>
<td>13 hours before start of infusion</td>
</tr>
<tr>
<td></td>
<td>50 mg</td>
<td>IV</td>
<td>20 minutes before start of infusion</td>
</tr>
</tbody>
</table>
OUTCOMES METHOTREXATE DESENSITIZATION

Patient tolerated next course of **16 steps desensitization** without side effects

Continued on 16 step protocol **without side effects** for each treatment

**Completed** chemotherapy courses

**Remission**
Background: Rapid desensitization, a procedure for graded drug administration, allows for the safe readministration of a medication after certain types of hypersensitivity reactions (HSRs) and is indicated in cases in which there are no reasonable therapeutic alternatives. The use of rapid desensitization for HSRs to mAbs has not been validated.

Objective: We sought to describe our experience with rapid desensitization to mAbs, including rituximab, infliximab, and trastuzumab.
MECANISMS OF MONOCLONAL ANTIBODIES HYPERSENSITIVITY REACTIONS

Hipersensibilidad tipo I
Activación de Basófilos
Activación de complemento
Tormenta de citoquinas
Activación de receptores
Excipientes
Papel de IgG anti AcMo

Desensibilización
CETUXIMAB
## INITIAL REACTIONS

### TABLE II. Patient characteristics

<table>
<thead>
<tr>
<th>Agent</th>
<th>Age/sex</th>
<th>Indication</th>
<th>Atopy</th>
<th>Reaction</th>
<th>Skin test result</th>
<th>No. of desensitizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>28/F</td>
<td>Breast cancer</td>
<td>Yes</td>
<td>Re-exposure</td>
<td>+</td>
<td>8</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>37/F</td>
<td>Breast cancer</td>
<td>Yes</td>
<td>Re-exposure</td>
<td>+</td>
<td>10</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>52/F</td>
<td>Breast cancer</td>
<td>Yes</td>
<td>Re-exposure</td>
<td>+</td>
<td>11</td>
</tr>
<tr>
<td>Infliximab</td>
<td>20/F</td>
<td>RA</td>
<td>Yes</td>
<td>5th</td>
<td>+</td>
<td>2</td>
</tr>
<tr>
<td>Infliximab</td>
<td>22/M</td>
<td>JRA</td>
<td>No</td>
<td>7th</td>
<td>+</td>
<td>2</td>
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<td>23/M</td>
<td>RA</td>
<td>Yes</td>
<td>7th</td>
<td>+</td>
<td>3</td>
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<td>No</td>
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<td>9</td>
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<td>8</td>
</tr>
<tr>
<td>Rituximab</td>
<td>64/F</td>
<td>NHL</td>
<td>No</td>
<td>4th</td>
<td>ND</td>
<td>2</td>
</tr>
<tr>
<td>Rituximab</td>
<td>23/F</td>
<td>SLE</td>
<td>Yes</td>
<td>Re-exposure</td>
<td>ND</td>
<td>2</td>
</tr>
</tbody>
</table>

*Re-exposure is defined as reaction on re-exposure after a prolonged, well-tolerated course.*

RA, Rheumatoid arthritis; JRA, juvenile rheumatoid arthritis; IBD, inflammatory bowel disease; NHL, non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; ITP, idiopathic thrombocytopenic purpura; FL, follicular lymphoma; BMT, bone marrow transplantation; ND, not determined; SLE, systemic lupus erythematosus.

New biological agents
Evaluation for desensitization to monoclonal Abs

- Allergy evaluation
  - Immediate reaction suggesting type I HSR
  - Desquamation
    - Skin blistering
    - Serum sickness
- Skin testing
  - Moderate - Severe reaction?
    - Standard infusion +/- premedication
    - Desensitization
    - Avoid medication

Figura 29: Sintomatología por cada grupo farmacológico durante la reacción inicial: en el eje Y se observa el porcentaje de pacientes que presentaron cada uno de los síntomas indicados en el eje X durante la reacción inicial.

Tito Rodríguez Bouza, “Modelo predictivo in vitro de desensibilización rápida mastocito-IgE: aplicación clínica a quimioterapicos, anticuerpos monoclonales, antibióticos y alimentos en pacientes con anafilaxia” Tesis Doctoral, Universidad de Alcalá de Henares, 2011.
SEVERITY OF INITIAL REACTIONS TO MONOCLONALS AND REACTIONS DURING DESSENSITIZATION

STEP AT WHICH REACTIONS OCCUR DURING MONOCLONAL AB DESENSITIZATION

SEVERITY OF THE REACTIONS DURING DESENSITIZATIONS OVER MULTIPLE DESENSITIZATIONS

Reactions over multiple desensitizations

Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment.
Safety of 2355 rapid desensitizations for Chemotherapy and Monoclonal Antibodies from 2007-2010 at BWH/DFCI

(MANUSCRIPT IN PREPARATION 2013)
Adding prostaglandin blockade (ASA) and leukotriene receptor blockade (montelukast) improved the tolerance and safety of reactions during desensitizations.
Figure 4

<table>
<thead>
<tr>
<th>Group</th>
<th>Metastatic = no</th>
<th>Metastatic = yes</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>52</td>
<td>353</td>
<td>405</td>
</tr>
<tr>
<td>Desensitized</td>
<td>94</td>
<td>77</td>
<td>171</td>
</tr>
<tr>
<td>Total</td>
<td>146</td>
<td>430</td>
<td>576</td>
</tr>
</tbody>
</table>

**Product-Limit Survival Estimates**

![Graph showing survival probability over survival time with two lines representing different groups.](attachment:image.png)
SELECTED PUBLICATIONS


Feldweg AM, Lee CW, Matulonis UA, Castells M. **Rapid desensitization for hypersensitivity reactions to paclitaxel and docetaxel: a new standard protocol used in 77 successful treatments.** Gyn Onc 2005; 96(3):824.


Castells MC et al. **Hypersensitivity Reactions to chemotherapy:Outcomes and safety of rapid desensitizations in 413 cases** J All Clin Immunol 122:574, 2008

Breslow R et al **Acetylsalicylic acid and montelukast block mast cell mediator-related symptoms during rapid desensitization** Ann All Clin Immunol 2009


Castells Editor Springer Humana Press **Anaphylaxis and Hypersensitivity Reactions** 2011

Sancho et al. **Rapid IgE desensitization is antigen specific and impairs early and late mast cell responses targeting FcεRI internalization** EJI 2011
DESENSITIZATION PROGRAM
This specific course, provides a deep overview of pathophysiology, underlying predisposing conditions and treatment of anaphylaxis, as well as a true update about the rapid desensitizations for the treatment of anaphylactic reactions to antibiotics, chemotherapy, and monoclonal antibodies as a new frontier in providing first line therapy for patients with cancer, cystic fibrosis, and other life-threatening conditions.

**16 November**

**Morning**
Sensitization / Desensitization Mechanisms
New concepts of Anaphylaxis
Antibiotics and other drugs induced Anaphylaxis

**Afternoon**
Practice Management in a Desensitization Unit
Rapid Desensitization for Antibiotic, NAID's and others

**17 November**

**Morning (¢)** Specially interesting for Oncologists
Drug Desensitization in the Management of Allergy and Anaphylaxis to Chemotherapeutic Agents and Monoclonal Antibodies

**Afternoon**
Case studies in drug desensitization: Discussion of real cases provided by audience (deadline to send them, October 15th)

**Presenters:**
Mariana Castells, MD.,Ph.D., and a panel of experts, most of them, trained in the Brigham and Women's Hospital. Harvard Medical School in Boston. USA.

**Official languages English & Spanish (translator will be able all the meeting)**

**LIMITED CAPACITY**

**Registration and more information:**
http://www.standingtours.cat
Email: mcampos@standingtours.cat