Trends-in-Medicine

October 2006
by Lynne Peterson

Quick Pulse

Trends-in-Medicine
Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

INFLAMMATION RESEARCH ASSOCIATION

Baltimore, MD
October 15-19, 2006

More than 300 researchers from pharma and biotech industries and academia attended this biennial conference on inflammation. The focus this year was on cardiovascular disease, fibrosis, and novel anti-inflammatory agents. The poster considered to have the greatest therapeutic relevance was on Praecis' PPI-2458, an oral MetAP2 inhibitor for rheumatoid arthritis (RA). The runner-up was a poster by an Array BioPharma researcher on ARRY-371797, an aerosol p38 inhibitor.

CARDIOVASCULAR DISEASE

The role of inflammation in cardiovascular (CV) disease got a lot of attention at the meeting. Inflammation is present in cardiovascular disease, but the key questions posed were:

- Will reducing inflammation really have an impact on CV disease?
- What's the clinical utility of inflammatory markers?
- Are inflammatory markers useful for screening, and if so, should everyone over 25 or everyone over 50 be screened?
- Are inflammatory markers a target for therapy? Should a certain CRP level be targeted like LDL and blood pressure?
- Can people be identified who don't meet the criteria for therapy?

Dr. Peter Libby, Chief of Cardiovascular Medicine at Brigham and Women's Hospital in Boston, said CRP has "risen to the top of the pack" as a biomarker of CV risk because it is a stable, chemically reliable, standardized, convenient, and inexpensive assay, and because it has a long half-life and no diurnal variations. He said it appears that lowering CRP correlates with improved vascular risk (and events), but added, "We are not ready for widespread CRP screening yet."

Dr. Libby said statins probably have some direct anti-inflammatory effect that is not from lipid lowering. PPAR agonist also may have an anti-inflammatory effect outside of any effect on LDL or HDL.

Asked if there is evidence from RA patients that CV risk is reduced in patients on an anti-TNF, Dr. Libby said, "I don't think we can get reliable evidence from those patients because so much else is going on with them…What we need are bio-markers to use in clinical trials, and those are being hotly debated within the industry at this point."

PAI-1 may be an important CV biomarker. Dr. Douglas Vaughan of Vanderbilt predicted that PAI-1 inhibitors will be of therapeutic value in the prevention and

treatment of a variety of human conditions, "We find that PAI-1 impacts on the accumulation of macrophages in animal fat. Almost all diabetics have high PAI-1 levels. Individuals with insulin resistance with elevated PAI-1 for years or decades have an increased CV risk." He said there is also a relationship between PAI-1 and atherosclerosis, adding, "There are many Americans with high PAI-1 who are at increased risk of coronary occlusion. Absolute PAI-1 deficiency is very rare in humans; Mother Nature designed us to have moderate levels of PAI-1…Transgenic expression of a stable form of human PAI-1 is associated with a variety of pathologies that are suggestive of human disease…This suggests that PAI-1 excess alone is sufficient to promote coronary thrombosis, amyloidosis, polycystic ovaries, etc…PAI-1 deficiency protects against fibrosis in most tissues…High levels of PAI-1 are probably pro-thrombotic…We would like to see if plasma PAI-1 predicts CV disease and events. We think there might be a protective effect in plasma."

Dr. Renu Virmani, a pathologist with the non-profit firm, CV Pathology, reviewed the causes of human coronary thrombosis:

- 60%-70% are **plaque ruptures**.
- 30%-35% are **plaque erosions**. She said this usually occurs in younger patients, especially women <age 50.
- 2%-7% are **calcified nodules**. She said these are very, very rare.

Human Coronary Thrombosis

Measurement	Ruptured thrombus	Thrombus erosion	Calcified nodules
Gender	More males	Males=females	More male, older
Shape	Eccentric	Usually eccentric	Usually eccentric
Stenosis	Greater % stenosis	Lesser % stenosis	Stenosis variable
Thrombus in AMI	65%-75%	25%-35%	---
Thrombus in sudden cardiac death	60%	35%	2%-5%

FIBROSIS

Fibrosis is a major cause of morbidity and mortality worldwide. In fact, fibrotic liver disease is the 8th most common cause of mortality. In the developed world, 45% of all deaths are attributed to fibroproliferative disorders – asthma, IPF, heart disease, kidney disease, cancer metastasis, chronic transplant rejection, autoimmune disease, liver disease, and sclerosis.

Dr. Don Rockey, a liver doctor from the University of Texas Southwestern, pointed out that obesity leads to fatty liver, which leads to liver inflammation, which ultimately leads to cirrhosis. He called this "an epidemic that is just about to hit us in the U.S." He said endothelins, PPARs, the hepatitis B treatments lamivudine (GlaxoSmithKline's Epivir) and adefovir (Gildead's Hepsera) all are being investigated, adding, "It does appear we can actually abrogate the fibrotic response…I think we can reduce fibrosis." Dr. Rockey said the ideal anti-fibrotic would be stellate cell specific, safe, easy to administer, and inexpensive.

The moderator at a session on fibrosis referred to several themes:

- The paradigm in which injury leads to inflammation, which then leads to fibrosis is typical across many biologic systems, though there are likely to be subtle, specific differences depending on organ type.
- There are several interesting pathways, particularly IL-13. Thomas Wynn PhD of the National Institutes of Health (NIH) said that researchers now believe that a lot of Th2 cytokines play a role in fibrosis over time, but that IL-4 and IL-5 also play a role, and "you can get a fairly significant IL-12 response." Wynn said IL-13 is a better route of blocking fibrosis than IL-4, and it looks like eosinophils are a source of IL-13. He added, "We learned recently that IL-21 can have a pro-fibrotic role."
- In some cases, inflammation may actually be beneficial, which he said was "very surprising" to him.
- Vectors include fibroblasts, fibrocytes, and epithelial mesenchymal transition (EMT) – and more will be heard about EMT in fibrosis.
- Fibrosis is truly a therapeutic unmet need.

Among the possible anti-fibrotic approaches are:

- Reduce or remove the primary injury.
- Block matrix synthesis or stimulate matrix degradation.
- Inhibit stellate cell activation.
- Stimulate stellate cell apoptosis.
- Block effects of stellate cell activation – fibrogenesis, contractility.

In 2015, Dr. Rockey said management of liver fibrosis will end up being a "cocktail" much as hypertension is treated today:

1. Fibrosis progression risk assigned based on a combination of clinical/genetic/lab markers.
2. Antiviral therapy instituted.
3. Based on risk of fibrosis, one or more anti-fibrotic drugs prescribed.
4. Non-invasive markers followed for response.

Where is the field going and where does it need to go? A speaker said there is need for:

- A better understanding of the natural history of this disease, "Most agree this is a long process, but we don't have good natural history data or good pathological clinical correlates. Whether the FDA envisions fibrosis alone as an outcome is not clear."

- Ways to measure fibrosis. He predicted the field will probably transition to surrogate markers, probably serum markers.
- Translation to the clinic – to get some therapies in the clinic so patients with fibrotic disease can be treated.

NOVEL ANTI-INFLAMMATORY AGENTS

Anti-IL-32

Researchers in the Netherlands presented a poster suggesting that IL-32 may be a novel therapeutic target in autoimmune disease like RA. They reported that IL-32 is a potent inducer of ongoing inflammation. They found that IL-32 is highly expressed in RA synovial tissue biopsies, and a strong association with TNF, IL-1β, and IL-1 was noted. When IL-32 was injected in naïve mouse knee joints, it reduced joint inflammation, with pronounced influx of inflammatory cells and cartilage damage. TNF deficient mice showed that IL-32 driven joint swelling was completely TNF dependent. IL-32 also showed a "remarkable" synergistic effect on cytokine production with LTR/NOD ligands, both *in vitro* and *in vivo*.

p38 inhibitors

Researchers generally were not very optimistic about this class of drug. They pointed to several failed attempts, noting that CNS, rash, and liver toxicities have been seen with different agents. One researcher suggested that making a safe p38 will require greater selectivity, but the greater the selectivity, the larger the molecule – and then it either won't cross the blood brain barriers, can't be feasibly manufactured, or both. Other comments included:

- "The first-generation p38s were too 'dirty' – too non-selective."
- "So many companies are looking at p38s that it is hard to believe we won't solve the problems."
- "I don't think you need high specificity. Selectivity is not what is driving the side effects. I think the p38 side effects are all off-target cytokine activity. There is not one unifying toxicity to support a mechanism-based toxicity."

If anything works, several sources predicted it may be Array BioPharma's aerosol p38 (see ARRY-371797), but they were not particularly optimistic about the outlook for that agent. Researchers stressed the difficulty of getting an inhaled drug through the regulatory process, and an Array source said the company needs a partner with experience in inhaled drugs to pursue ARRY-371797.

ABBOTT LABORATORIES

Dr. Carolyn Cuff of Abbott presented rat research on whether anti-TNF antibodies are effective in a pre-clinical model of asthma and on what pre-clinical endpoints translate into clinical efficacy. She reported that there was efficacy in a murine model of ovalbumin-induced asthma, and the effect on airway hyper-responsiveness appears to translate from pre-clinical to clinical efficacy, but the mechanism for efficacy is still unclear. Asked if the thousands of RA patients treated with an anti-TNF who also have asthma have seen any benefit to their asthma from the TNF therapy, she said, "I don't know of anything that's been published. The number of RA patients with asthma is not high enough to gain insight into that question."

ACTIVE BIOTECH/AVIDEX'S RhuDex

Preclinical data were presented on this co-stimulation inhibitor, a low-molecular weight antagonist of CD80/CD28 interaction. Dr. David Howat of the U.K. said the concept was validated by Bristol-Myers Squibb's Orencia (abatacept). RhuDex is being developed first in RA, and then will be explored in Crohn's Disease, MS, and psoriasis. He said it has shown good preclinical safety and toxicology in the two completed Phase I trials. The issue, however, is efficacy. Apparently, gastric acid neutralizes RhuDex, and the company looked at buffering it with ranitidine, etc. Dr. Howat said, "It is poorly absorbed without the use of (something) to neutralize gastric acid in the stomach."

AMGEN

- **IL-7.** Amgen researchers presented a poster on some basic science work on antibodies against IL-7 and IL-7Rα. Asked what Amgen might do with this, a researcher said the company is looking at whether an anti-IL-7 might have utility in Enbrel (Amgen, etanercept) non-responders, but the work is still in the discovery stage.
- **Anti-mIL-17 monoclonal antibody.** Amgen also presented a poster on an anti-mIL-17 monoclonal antibody in an animal model of MS. In mice, this anti-mIL-17 antibody significantly delayed disease onset, reduced disease incidence, and reduced mean clinical scores vs. an isotype control Mab.

ARRAY BIOPHARMA

- **ARRY-371797.** This highly selective p38 mitogen-activated protein (MAP) kinase inhibitor has shown efficacy in preclinical models of cancer and arthritis when administered to the lungs by intratracheal instillation aerosol. An IND filing is expected before the end of the year. At the least, the company has shown proof-of-principle that aerosol delivery is possible, with a treatment effect up to 24 hours.

Only ~10% of the compound is metabolized in the lungs; ~90% of it reportedly is swallowed, raising the question of whether any effect is actually from systemic exposure instead. However, researchers reported that charcoal studies indicate the activity is due to pulmonary exposure, not systemic absorption.

Researchers reported that ARRY-371797:

- Significantly decreased phosphorylation of pHSP27 for 12 hours, which then rebounds, suggesting BID dosing.
- C_{max} concentrations in the lung are ~50-fold greater than in plasma (148 ng/mL).
- Exposure (based on AUC) in the lung is ~75-fold greater than exposure in the plasma.
- The high dose is 8.5 mg/kg.
- Can be feasibly delivered to the lung.
- Blocks both p38 *in situ* and the resulting inflammation.
- Has substantial and durable effects.
- Activity is due to pulmonary exposure and not systemic absorption.

NOTE: Array reportedly has kicked around the idea of local delivery of ARRY-371797 for psoriasis.

➢ **ARRY-438162.** President and Chief Scientific Officer Kevin Koch reported the first clinical data on this oral MEK1/2 inhibitor, which entered clinical trials earlier this year. While Array licensed three compounds to AstraZeneca for cancer therapy, Array retained the rights to other indications for these compounds, which could include pain, stroke, diabetes, COPD, and inflammation. Preclinical studies demonstrated that ARRY-438162 is potent, selective, well tolerated, and effective in animal models of inflammation.

- Mean C_{max} = 234 ng/mL
- T_{max} = 1.25 hour
- Half-life = 7.57 hours

ARRY-438162 vs. Other Drugs

Drug	IC50 (nM)
Cox-2 inhibitor	2.0
ARRY-371797	4.7
ARRY-614	1.2
ARRY-438162	7,237.2

In rat studies of an arthritis model, QD dosing with ARRY-438162 appeared more efficacious than Enbrel or ibuprofen, and it was additive or synergistic to methotrexate, with effects on paw diameter, paw weight, spleen weight, and markers of inhibition of bone resorption. Koch said, "(ARRY-438162) has shown excellent efficacy in several (animal) models and exceeds the efficacy of market drugs such as indomethacin and Enbrel."

A Phase Ia study in healthy volunteers tested 5 mg - 40 mg doses, and additional dosing studies are underway. These are using a liquid suspension, reported to "ease manufacturing issues," but a capsule formulation has been developed for future trials, and commercial synthesis reportedly is "in place." There were no drug-related serious adverse events up to 20 mg/day QD for 14 days, and inter- and intra-patient variability was described as "moderate." However, Koch noted that there are not enough data to say whether this drug will or won't have an effect on inflammation. He said they expect to see adverse events "at some point," adding, "At 20 mg BID we are beginning to see hints, but they are mild at this point. I don't know how much higher we can go. We are continuing to dose escalate."

Other Phase Ia findings included:

- Good inhibition (42%-60%) of TNF-α at 1-2-4 hours.
- IL-1b was affected "profoundly," with up to 80%-90% inhibition, and even out to 24 hours there was inhibition of ≤40%. There was consistent and robust inhibition of tPA-induced IL-1 production by whole blood for at least 4 hours post-dose.
- No inhibition of IL-1RA or TNFRII levels.

A 4-week Phase Ib is expected to start this month in combination with methotrexate in RA patients with stable disease, looking at safety, tolerability, and ACR20, though 28 days may be too early to see an effect on ACR20. Dosing may be either QD or BID, and the company is still evaluating which will be used. Long-term toxicology testing also has been initiated, and Phase II is scheduled to start in summer 2007. In addition to RA, several other indications are "under evaluation."

ARZNEIMITTEL GMBH'S tripeptide

Researchers for several other pharmas expressed interest in this IL-1β-derived tripeptide for treatment of inflammatory bowel disease. In a mouse model of inflammatory bowel disease, it significantly improved the course of colitis, reduced weight loss, and speeded recovery. It was effective both prophylactically but also as a therapeutic, which investigators called surprising.

ATHEROGENICS/ASTRAZENECA'S AGI-1067

AtheroGenics researchers were optimistic about the outlook for this drug, despite its rocky history. They presented a poster on AGI-1067 which showed a mechanistic framework for understanding the anti-atherosclerotic and anti-inflammatory properties of the drug. They showed that AGI-1067 selectively inhibits endothelial cell TLR4-mediated, but not IL-1R-mediated, activation of p38 and JNK MAP kinases, and expression of cytokines and chemokines. They concluded that the data suggest that modulation of the endothelial intracellular redox state by AGI-1067 inhibits the redox-sensitive ASK1/p38-JNK pathways.

COMBINATORX

This company, which is trying to develop new medications by finding synergistic combinations of already approved (generally generic) drugs, was not represented at the Inflammation Research Association meeting. So far, five product candidates

targeting multiple immuno-inflammatory diseases and cancer are being tested. Three selective steroid amplifiers are in Phase II development for immuno-inflammatory diseases. Each consists of a reduced-dose corticosteroid combined with a different second active ingredient. The company says preclinical studies suggest the combination enhances the steroid's anti-inflammatory and immuno-modulatory activity without a comparable increase in adverse side effects.

- **CRx-102 (prednisolone + dipyridamole).** This lead compound is a combination of a steroid and an anti-platelet agent. A small Phase I trial looked promising in hand osteoarthritis (OA). Data from an RA trial are expected soon, and a Phase IIb program is expected to start early next year.
- **CRx-139 (prednisolone + SSRI).**
- **CRx-170 (budesonide + nortriptylline).**

Researchers for several big pharmas who were questioned about CombinatoRx said they had not heard about it or its approach, but they were dubious that it was commercially feasible. Several pointed to NitroMed's recent failure to successfully market BiDil, a combination of two generic drugs for hypertension.

- "A couple of (our) guys believe it will be successful, but so far we haven't seen any real successes."
- "I was told to take a look at it, and I'm watching it, but I'm not optimistic. I don't think it will work, at least not in any (commercially) useful way."

DR. REDDY

Dr. Reddy has an active drug development group. It is investigating MMPs and proteoglycans, and it is starting to look at arthritis and Crohn's Disease. A researcher said, "We are most hopeful about our cardiovascular compound, RUS-3108, which finished Phase I and is starting Phase II...We also have a compound for RA which we hope could go to the clinic next year. We are looking for a partner for that."

Proteomic Markers of 2 Arthritis Therapies

Markers of methotrexate activity	Markers of Enbrel activity
Adam 23	Ferritin
Alpha internexin	Cathepsin B
Calreticulin	Sciellin
YME111	Annexin A10
Serpin B10	IL-1-δ
Small inducible cytokine B14	Small inducible cytokine A24
	Small inducible cytokine B13
	Insulin-like growth factor binding protein 5
	SOCS-4

Dr. Reddy researchers presented a poster on their serum proteomic study of biomarkers relevant to arthritis. In animals, significant differences were seen in serum protein of arthritis compared to normal controls, and there were differences in the markers between methotrexate and Enbrel.

- **DRL-13156.** This looks promising in both RA and OA. A poster reported this synthetic cytokine modulator shows good inhibition of paw edema in models of acute inflammation and arthritis. Researchers said it has:
  - Cytokine inhibition which Pfizer's Celebrex (celecoxib) doesn't have.
  - Cartilage protection, as shown by serum markers.
  - Superior joint protection to oral synthetic DMARDs and methotrexate.
  - No immunosuppressive effects.
  - A significant decrease in joint damage in an OA model.

JOHNSON & JOHNSON'S PEG-TCA

This complement inhibitor is still in preclinical testing, and J&J does not plan to develop it because the company believes the market is too small, but J&J will offer it to academia to study, and J&J is willing to partner with another company, particularly in lupus – but J&J is not interested in selling it. The Army may be interested in it for use in trauma.

KEMIA'S KC-706

This oral p38 kinase inhibitor has completed a Phase I trial and two Phase IIa trials are ongoing outside the U.S. (one in RA and one in CV disease). The Phase I data have not been presented yet, but the Phase II data are expected in summer 2007, and a researcher said the company would disclose the entire program at that time.

A poster presented preclinical data on another p38, KR-RC1. Therapeutic activity was seen in both mouse and rat models of acute and chronic inflammation, with substantial inhibition of paw edema. Collagen-induced arthritis in mice was significantly inhibited at 10 mg/kg and 30 mg/kg, and there was evidence of disease-modifying activity in that model by histologic evaluation of joints.

Kemia also is in preclinical testing of a p38 for mild-to-moderate psoriasis as a topical agent.

LILLY

Jonathon Sedgwick, Director of Bone and Inflammation Research, discussed IL-23/IL-17 biology. He pointed out that IL-23 is very key in the development of Th17 cells.

MERCK'S MK-0812

Dr. Agustin Melian, director of clinical research at Merck, explained why this oral small molecule antagonist of CCR-2 failed. A 12-week, 149-patient, randomized, double-blind, parallel group trial in RA testing two doses of MK-0812 (0.4 mg and 10 mg) was stopped early after an interim analysis found no benefit from the drug – and no likelihood of a positive outcome if the trial were continued. Adverse events trended higher with high dose MK-0812 than placebo – and there was no clinically meaningful difference in ACR20 response rates with either dose. Merck concluded MK-0812 most likely is not effective in RA, though it is possible they didn't treat patients long enough or with a high enough dose. Dr. Melian said, "A number of different companies are working on this target in different indications. We looked at RA, MS, and vascular disease…An abstract is coming out at the American College of Rheumatology, but I don't think (those findings) are different from here."

PDL BIOPHARMA'S N-297A

This FC-modified anti-human CD-3 monoclonal antibody may have utility in MS. PDL researchers reported that in mice, two daily 10 µg/mouse doses of N-297A, given at the onset of disease, caused a rapid disappearance of T-cells from peripheral blood, lymph nodes, and the spleen. Cerebral spinal fluid also showed a decrease of several pro-inflammatory cytokines.

PHARMACOPEIA DRUG DISCOVERY'S PS-608504

Matthew Sills, Director of Pharmacology, discussed this oral JAK-3 inhibitor that is being investigated for transplant rejection and which also may have therapeutic potential for psoriasis, multiple sclerosis, and asthma.

PFIZER

- **PH-089.** Pfizer researcher Robert Mourey reported on the pharmacological characterization of this oral small-molecule inhibitor of MK-2. The drug inhibited TNF-α production, and in a rat arthritis model BID administration reduced paw swelling at Day 21. This is the first orally-active small molecule MK-2 inhibitor with efficacy in a rat arthritis model.

PH-089 in Rat Arthritis Model

Dose	Paw value	Paw swelling
Normal	~ 1.4 ml	---
30 mpk	~ 2.0 ml	Down 38%
60 mpk	~ 1.7 ml	Down 55%
120 mpk	~ 1.5 ml	Down 74%

- **PF-03442942.** This is an inhibitor of a newly identified anti-apoptotic gene, Hrd1, which was test explored in RA. Dr. Lakshman Rajagopalan of Pfizer said it hasn't looked very potent so far, but he said it is still early, and they have shown that it can inhibit IL-6 and IL-8.

- **MMP inhibitors.** A Pfizer researcher discussed new tools to assess the role of collagenase in biology and disease. He said Pfizer spent 10 years trying to develop an MMP, and there is still no MMP inhibitor in osteoarthritis. Pfizer researchers found MMP13 is the only MMP with the right specificity. He suggested there may not be any commercial viability for these agents given the development timeline.

PRAECIS PHARMACEUTICALS' PPI-2458

William Westlin, Vice President of Preclinical Research, reported preclinical data on this oral, small molecule, methionine aminopeptidase type-2 inhibitor, which is currently in Phase I development for non-Hodgkin's lymphoma and all solid tumors. He said it also has shown potent disease modifying activity in four distinct animal models of arthritis. With every-other-day administration at 5 mg/kg and 10 mg/kg, it completely inhibited the target enzyme, MetAP-2. He added, "The highest dose (10 mg/kg) didn't look quite as good as dexamethasone on CT, but it was nearly as good on bone erosions…PPI-2458 inhibits cartilage erosion *in vivo* in a rat PGPS arthritis model."

Praecis is hoping that an ongoing Phase II oncology trial will serve as a safety database for an aggressive RA trial. The company expects to seek an IND in RA in early 2007. The main downside to this drug appears to be a ~25% reduction in blood T-cells, but there is also some diarrhea at the lowest dose, and a decrease in body weight gain in animals.

Additional data will be presented in November 2006 at EORTC in Prague, the Czech Republic.

PROCTER & GAMBLE'S PG-1012528

This oral LCK inhibitor has been dropped by P&G. A researcher said, "It works, but there are probably others that are better – and P&G isn't doing any more drug discovery. In fact, he said P&G doesn't plan to patent PG-1012528.

P&G is interested in in-licensing compounds – but not biologics because that field is too crowded, there are mostly injectables, and they are expensive. A source said, "For P&G, it has to be an oral."

RIGEL PHARMACEUTICALS' R-935788

Dr. Elliott Grossbard, Senior Vice President of Medical Development, said the company looked at the parent of this syk kinase, R-940406, and "decided it might not be useful in a disease as mild as (allergic) rhinitis." Instead, they are investigating R-935788, a prodrug of R-940406, in other indications. Pfizer licensed the rights from Rigel to a related drug as an inhaled therapy in asthma. Dr. Grossbard said, "Eventually the risk:benefit profile has to work, and I think we will be in better shape in more serious illnesses…R-940406 is

like a brick, very insoluble. It would not have been a viable formulation for clinical development…My job is to find some use for this thing (R-935788) before we run out of money."

A tablet formulation of R-935788 has been developed. The T_{max} is 1.08-1.29 hours, and C_{max} is 1560-7630 ng/mL.

Possible areas of development include:

- **RA.** This is the principal focus right now. So far, about 100 volunteers have been treated. Study 788-007 – a 12-week, 180-patient, U.S., randomized, double-blind, placebo-controlled trial of three BID doses (50 mg, 100 mg, and 150 mg) – is about a third enrolled.
- **Lupus.** In a mouse model of lupus, the drug increased survival substantially and reduced BUN and proteinuria.
- **ITP.** There also appears to be activity in ITP, but Dr. Grossbard said, "In our own study with hundreds of mice, we found it reduces thrombocytopenia…I'm satisfied there is an effect, but I don't know if we will do anything with this clinically…We will do a study in chronic, refractory ITP." That trial is expected to start in about 30 days. It will be an open-label, ascending dose study of three groups of 3-6 patients each.
- **Lymphoma.** The company plans to file an IND for lymphoma in November 2006.
- **Renal cell carcinoma.** Reportedly, the National Cancer Institute is interested in exploring this indication.

There is some reproductive toxicity with R-935788, so it may not be able to be taken by women of child bearing age. Dr. Grossbard said, "This is not a compound that children with runny noses were going to take…but for RA, safety should be okay...The safety issue we see in animals is not severe or cliff-like, but it will be a delicate balance taking this through clinical programs."

There is also some "mild" transaminase elevation, which is reversible when the drug is stopped. Some leukocytopenia and neutropenia has also been seen. And half of one small group of healthy volunteers developed orthostatic diastolic hypertension (an increase of 15-20 mmHg).

SERONO'S AS-602801

This is an c-Jun-N-terminal kinase (JNK) inhibitor for multiple sclerosis (MS) that Serono did ***not*** talk about at ECTRIMS last month. This small molecule would be a first-in-class and is being developed both as an oral and an injectable. It has shown promise in preclinical studies and Phase I testing has begun.

Jean-Pierre Gotteland, head of medicinal chemistry at Serono, said he believes that AS-602801 may act at two different stages of MS: as both an anti-inflammatory and a neuro-protective. He explained that JNK2 production is significantly increased in relapsing remitting MS (RRMS), and AS-602801 has:

- Good selectivity.
- Low solubility in buffer but high solubility in water or saline.
- Moderate permeability.
- No significant CYP450 inhibition and no hErg issue.
- A good distribution pattern with no accumulation.
- Good oral bioavailability with high plasma exposure.
- Linear PK for doses from 80 mg - 320 mg.
- T_{max} of 1.0-2.0 hours.
- Half-life of 16 hours, which is consistent with BID dosing.

Compared to Novartis's oral MS therapy in development, fingolimod (FTY-720), Gotteland said AS-602801 appears to have similar efficacy but a much cleaner safety profile – no ALT elevation, edema, blood pressure effects, etc. However, a slight bronconstriction was seen in rats and guinea pigs at high doses, but no CNS or CV side effects. He said, "In the mouse, we see a clear effect (with AS-602801) on the onset of disease and a delay in progression."

A randomized, double-blind, placebo-controlled Phase I study in 32 healthy males, tested oral doses from 8 mg - 640 mg. Gotteland reported it was safe, well-tolerated up to 570 mg, with no clear evidence of an adverse event dose relationship and no clinically significant changes in vital signs, laboratory safety tests, etc.

Another 14-day, randomized, double-blind, placebo-controlled safety and tolerability study in 40 healthy males is just being unblinded, so results were not presented at this meeting. Patients were dosed BID.

WYETH'S TMI-005

This drug failed in RA, but Dr. Ian Gourley of Wyeth explained what the company learned from this.

In Phase I studies, TMI-005 appeared safe, but no efficacy was seen. The company expected to see about a 30% improvement in ACR20 at three months in a 390-patient, randomized, double-blind, placebo-controlled, worldwide Phase II trial in which TMI-005 (150 mg - 450 mg) was co-administered with methotrexate. However, TMI-005 was no more effective than placebo, and at the higher dose trended to be worse on CRP, sedimentation rate, etc. Furthermore, 12 patients had ALT >2.5xULN.

Wyeth did an exploratory analysis of the patient blood samples that had been taken. Dr. Gourley said an RNA study found no explanation for the failure, but the plasma study did have one significant finding: "MDC (CCL22) showed significant elevation vs. baseline at Week 4. We don't know

the significance of that. It could be a random effect. Nothing we know about this drug that mechanistically would tie this in."

Dr. Gourley wondered if what happened with TMI-005 will prove to be a class effect with all TACE inhibitors. A Bristol-Myers Squibb researcher said DuPont had a TACE inhibitor in development that was terminated prematurely due to hepatic toxicity, and a follow-on TACE also showed no efficacy.

♦