enzyme-linked immunosorbent assay. CII specific proliferation of T cells derived from draining lymph nodes was assessed with thymidine incorporation assay.

Results: The smCDKI monotherapy suppressed arthritis, radiographic and histological scores of CIA dose-dependently. The therapeutic effects were observed without myelosupression. Both of IL-6R-Ab and ETN monotherapies were also effective. Their efficacy was further enhanced in the all scores when combined with smCDKI administration. Of note, the combination of smCDKI and ETN suppressed arthritis almost completely. Serum anti-CII antibody levels and CII-specific T cell proliferation were comparable among all the treated and control groups.

Conclusion: This is the first report demonstrating that combination of molecular targeting therapies exerted synergistic effects without increase in immune suppression. The smCDKI treatment combined with the anti-cytokine treatment might be more effective than anti-inflammatory monotherapy without increasing infection risks in treating RA. We hope that development of smCDKI as an anti-rheumatic drug will help to increase the remission induction rate in RA treatment without inducing infections.

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Novel Role For Ly6C$^-$ Monocyte Subsets and Joint Macrophages In Mouse Model Of Rheumatoid Arthritis. Alexander Misharin[1], Carla M. Cuda[2], Rana Saber[1], Angelica K. Gierut[3], G. Kenneth Haines III[4], Steffen Jung[5] and Harris R. Perlman[1]. [1]Northwestern University, Chicago, IL, [2]Northwestern University Feinberg School of Medicine, Chicago, IL, [3]Northwestern Med Faculty Found, Chicago, IL, [4]Yale University, New Haven, CT, [5]Weizmann Institute, Rehovot, Israel.

Background/Purpose: Monocytes and macrophages play a key role in the pathogenesis of rheumatoid arthritis. However, role of the individual subsets of monocytes and macrophages in the initiation, perpetuation and/or resolution of arthritis is unknown.

Methods: To uncover their role we utilized multiple strategies to deplete selective subsets of monocytes and macrophages in the K/BxN serum transfer arthritis mouse model: clodronate-loaded liposomes, diphtheria toxin and CD11b-DTR mice, aCCR2 antibody, adoptive transfer of monocytes.

Results: We found that contrary to the current dogma monocytes, and not neutrophils were necessary for initiation of arthritis. Moreover, we found that only non-classical Ly6C$^-$ monocytes were required for induction of arthritis, while classical Ly6C$^+$ monocytes were dispensable. Further, we identified that naïve mouse joint contains heterogeneous population of macrophages, which differ in their origin, turnover and function, namely tissue-resident macrophages and bone marrow-derived macrophages. Selective depletion of the tissue-resident macrophages accelerated development of arthritis, while depletion of bone marrow-derived macrophages had no effect on arthritis. While blood monocytes were necessary for initiation and development of arthritis, they were not necessary for its resolution. In contrast, tissue macrophages were crucial for the resolution, since their depletion delayed resolution of arthritis and was associated with increased histological joint damage.

Conclusion: These data suggest that unlike other models (myocardial infarction, infectious diseases) resolution of arthritis does not require second wave of monocyte recruitment into the joint, but rather dependent on a molecular rheostat within macrophages, which controls the switch of their phenotype from "proinflammatory/classically activated" to a "wound healing/regulatory". Phagocytosis of apoptotic neutrophils (efferocytosis) is potentially one of the mechanisms controlling this switch.

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Treatment Of Innate Immune Arthritis With a Toll-Like Receptor 7 Agonist Requires Type I Interferon. Maripat Corr[1], Tomoko Hayashi[2], Dennis A. Carson[2], Howard Cottam[3] and Joshua Yang[2]. [1]Univ of California-San Diego, La Jolla, CA, [2]UCSD School of Medicine, La Jolla, CA, [3]ucsd School of Medicine, La Jolla, CA.

Background/Purpose: We previously demonstrated that repeated administration of the low molecular weight Toll-like receptor (TLR) 7 agonist (1V136) substantially reduces arthritic inflammation in mice. Here we investigated the mechanisms contributing to this potent anti-inflammatory effect using the K/BxN passive transfer model of murine arthritis.

Methods: The following mutant strains were given arthritis with 150ul K/BxN serum intraperitoneally (ip) and treated with daily subcutaneous (s.c.) injections of vehicle or 150nmol 1V136: C57BL/6, *Tlr7*$^{-/-}$, *Ifnar1*$^{-/-}$, *kit*$^{W\text{-}sh}$ (Wsh), Pretty2, and *Stat1*. Bone marrow chimeric mice were generated by irradiating C57BL/6 and *Tlr7*$^{-/-}$ mice with 10Gy and injecting these recipients with 10^7 donor bone marrow cells (BM). To assess the effects on vascular permeability mice were injected with 150ul K/BxN serum i.p. and 1mg/kg Evans blue dye intraveniously. After sacrifice the paws were removed and incubated in formamide overnight and the absorbance of the supernatant at 600nm was measured. Complete blood counts were performed by the UCSD Animal Care Program Diagnostic Laboratory.

Results: The joint swelling and arthritis scores of K/BxN serum transferred arthritis was significantly reduced by daily injections of 150nm 1V136 s.c. in C57BL/6 (WT) mice (AUC 6.6 drug treated vs. AUC 0.38 vehicle treated, $P<0.001$). Radiation bone marrow chimeric mice were tested and in WT BM>WT mice paw swelling in 1V136 treated mice was significantly less than vehicle treated controls (AUC 3.3 vs 7.4, $P<0.01$), but not in the TLR7 BM>TLR7 mice (AUC 6.7 vs 7.1, $P>0.05$). In mixed chimeras the drug was effective in the WT BM>TLR7 mice (AUC 4.9 vs 7.4, $P=0.03$), but not in the TLR7 BM>WT (AUC 6.2 vs 7.0, $P>0.05$). These data suggested that TLR7 is necessary for the activity of the compound. Mice that were defective in STAT1 and type I IFN signaling were refractory to 1V136 treatment, implicating these molecules effector molecules in the mechanism of this drug treatment. The data using BM chimeric mice suggested that radiosensitive cells were primarily involved in the beneficial effects of 1V136. A single dose of 1V136 reduced plasma extravasation in the joints of mice that received K/BxN sera. Plasma extravasation in immune complex reactions is associated with mast cell degranulation and neutrophil recruitment. Two strains of mast cell deficient mice were tested: Pretty2 and kit$^{W\text{-}sh}$ mice. The kit$^{W\text{-}sh}$ mice were refractory to treatment (AUC 7.3 vs 5.6, $P>0.05$), but the Pretty2 mice responded to 1V136 (AUC 2.2 vs 7.5, $P<0.05$). In the Pretty 2 strain the c-kit mutation is also associated with a low level of circulating neutrophils. A single dose of 1V136 significantly decreased the circulating white blood cells in WT mice ($10.6+0.22$ vs $3.9+0.44$, $P<0.01$), but not IFNAR1 null mice ($11.77+0.7$ vs $10.8+0.5$, $P<0.05$). There was no effect in the platlet counts.

Conclusion: The joint inflammation and vascular permeability observed in the passive serum transferred arthritis were significantly attenuated by 1V136 treatment. The drug requires TLR7 on bone marrow derived cells, and an intact type I interferon pathway to be fully effective.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy: Efficacy and Safety of Novel Entities
Monday, October 28, 2013, 2:30 PM–4:00 PM

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Efficacy and Safety Of Subcutaneous Administration Of Tabalumab, An Anti-B Cell Activating Factor Monoclonal Antibody, In Rheumatoid Arthritis: Results From a Phase 3 Multicenter, Randomized, Double-Blind Study. Mark C. Genovese[1], Gregg J. Silverman[2], Paul Emery[3], Ramesh Gupta[4], Anne Gill[5], Wendy J. Komocsar[5], Melissa Veenhuizen[5], Li Xie[5], Pierre-Yves Berclaz[5] and Chin Lee[5]. [1]Stanford University, Palo Alto, CA, [2]NYU School of Medicine, New York, NY, [3]University of Leeds, Leeds, United Kingdom, [4]Private Practice, Memphis, TN, [5]Eli Lilly and Company, Indianapolis, IN.

Background/Purpose: Tabalumab is a monoclonal antibody that neutralizes membrane-bound and soluble B cell activating factor (BAFF). These interim analyses evaluated the efficacy and safety of 2 different subcutaneous (SQ) dosing regimens of tabalumab in RA patients (pts).

Methods: 1004 pts (ITT population) were enrolled in this phase 3, multicenter, randomized, double-blind study that evaluated 2 different SQ tabalumab doses (120 mg every 4 wks [120/Q4W] or 90 mg every 2 wks