

# Digital Vivarium™ Platform Enables Automated Drug Efficacy Assessment Correlated with Pathology in Rheumatoid Arthritis

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## Introduction

Vium has created a Digital Vivarium™ that uses an intelligent sensor and HD camera network along with computer vision, data algorithms, and cloud computing to improve *in vivo* research.

The number of therapeutics that can be simultaneously evaluated for efficacy in rodent disease models are frequently limited by labor-intensive key measurements that require the same technician for consistency. We used our Digital Vivarium™ to:

- create the automated, objective Vium Arthritis Index™ which continuously monitors function-related endpoints of disease severity
- provides additional health endpoints, such as breathing rate, overall activity, and circadian rhythms
- provides efficacy and health endpoints with limited human interaction
- allows real-time, remote data access over the internet to enable rapid decisions
- Retains data in auditable electronic and videographic records
- Enable more arms or compounds to be evaluated simultaneously

We validated automated disease scoring in a standard model of arthritis with an algorithm that captures salient motion metrics during the animals' active period to compute the Vium Arthritis Index™, which reproducibly correlated to disease pathology and was better at detecting mild disease pathology as compared to joint swelling. Here we demonstrate the platform was used to profile 9 re-purposed drugs at 3 different dose levels for efficacy.

## Materials and Methods

Experiments were conducted in Vium's AAALAC-accredited Digital Vivarium™ in accordance with the NIH Guide for the Care and Use of Laboratory Animals and were approved by Vium's Institutional Animal Care and Use Committee.

**Animals:** Female Lewis rats were randomized into study groups, such that all groups had similar baseline body weights and activity profiles prior to induction. Arthritis was induced via intradermal injections of porcine type II collagen in Incomplete Freund's Adjuvant (IFA) on study days 0 and 7.

**Treatment:** Rats were treated beginning on day 9 following induction with vehicle, Methotrexate (0.075mg/kg, PO, qd), Enbrel (10mg/kg, SC, q3d) or Dexamethasone (0.075mg/kg, PO, qd), or one of 9 proprietary re-purposed drugs.

**Vium Smart Housing™:** Cages are outfitted with sensors that stream data and environmental conditions 24/7. The Digital Vivarium collects, displays, and analyzes data continually in near real-time.

**Tracking and Measurement of Arthritis in Rats:** Data acquired from three independent replications of the CIA rat study were used to create and validate the Vium Arthritis Index™. Using optical flow analysis, video data was converted into continuous high temporal resolution activity summaries (Fig 1). The maximum speed of movements were extracted and aggregated by day for each animal. Aggregated activity on a given day was normalized to a baseline period and the ratio of aggregated activity to baseline activity was termed the Vium Arthritis Index™.

**Statistical analysis:** A one-way ANOVA was used to assess joint measurements, VAI, and onset day. Two-way ANOVAs were used to assess efficacy of drugs with groups and study days as the independent variables. *P* values < 0.05 were considered significant.

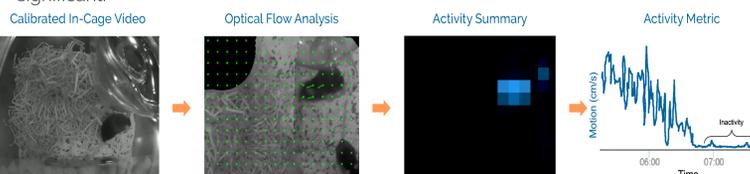


Figure 1: Data processing flow demonstrating how in-cage video of the animals' is transformed into the activity metric used to create the Vium Arthritis Index™.

## Vium Arthritis Index™

### Vium Arthritis Index™ tracks disease severity similar to conventional joint measurements

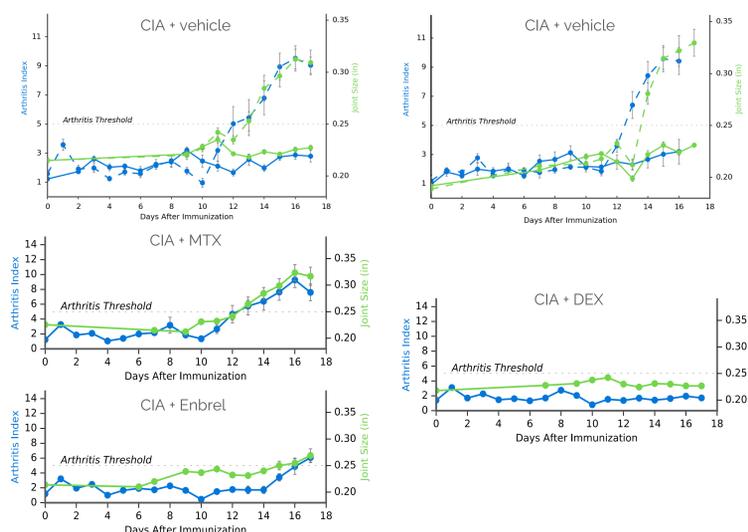


Figure 2: The Vium Arthritis Index (VAI; blue lines) tracks with joint size (green lines), a conventional assessment method of arthritis in control (solid lines in top two graphs), CIA-induced rats treated with vehicle (dotted lines in top two panels), methotrexate (MTX), Enbrel, or Dexamethasone (DEX). Arthritis threshold (dotted line) indicates the threshold at which the VAI and ankle joint sizes are significantly increased from baseline, signifying presence of arthritis. *n* = 9/group. Error bars are SEM.

### Disease severity measured by the Vium Arthritis Index™ at study end correlates with histopathology

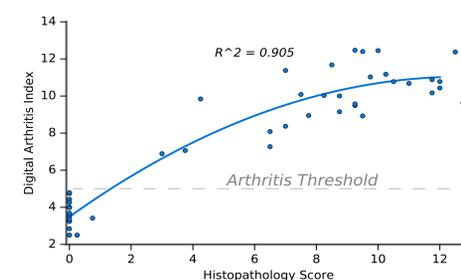


Figure 3: There is a strong positive correlation (*p* < 0.01) between the Vium Arthritis Index™ and histopathology. Shown are vehicle treated control and CIA-induced rats. Arthritis threshold (dotted line) indicates the threshold at which the VAI is significantly increased from baseline.

### Vium Arthritis Index™ tracks disease similar to conventional measures

Table 1: Summary statistics for disease course with SOC drugs

	Vehicle	MTX	Enbrel	DEX
<b>Arthritis Index</b>				
Incidence	9 of 9	8 of 9	7 of 9	0 of 9
Onset	13.3 ± 1.7	13.0 ± 1.8	16.1 ± 0.9*	N/A
Severity	9.7 ± 1.8	9.7 ± 3.3	6.8 ± 2.1*	2.4 ± 1.1*
<b>Joint Size</b>				
Incidence	9 of 9	8 of 9	5 of 9	0 of 9
Onset	12.8 ± 1.3	12.9 ± 1.1	15.6 ± 1.7*	N/A
Severity	0.33 ± 0.03	0.33 ± 0.05	0.27 ± 0.04*	0.23 ± 0.01*
<b>Histopathology</b>				
Score	7.4 ± 2.8	8.1 ± 3.8	2.6 ± 2.7*	0.1 ± 0.3*

Disease incidence, onset, and severity were calculated using either the VAI or joint measurements for CIA-induced rats treated with SOC drugs. The VAI identified 2 additional Enbrel-treated rats with arthritis than using conventional joint measurements. Histopathology scores for the rats were 0.5 and 1.5 indicating very mild disease. Values are average ± stdev. \**p* < 0.01 vs. CIA vehicle treated groups.

## High scale drug profiling with the VAI

### The Vium Arthritis Index™ was used to assess efficacy of 9 re-purposed compounds

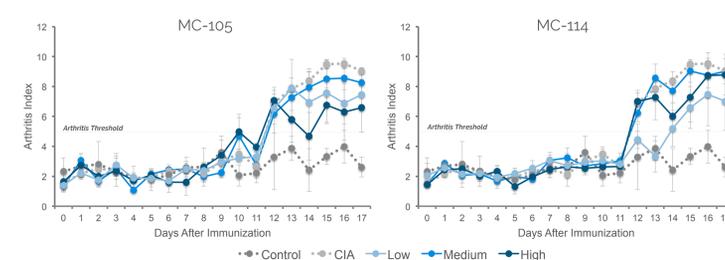


Figure 4: Nine compounds were identified as potential therapeutics for rheumatoid arthritis using a computational drug discovery engine. Shown are therapeutic efficacy profiles for 2 of the 9 drugs assessed. For MC-105, the arthritis index was significantly improved in the high dose (*p* < 0.01), whereas in MC-114, significant improvement in arthritis was seen in the low dose (*p* < 0.001). Arthritis threshold (dotted line) indicates the threshold at which the VAI are significantly increased from baseline, signifying presence of arthritis. *n* = 4 - 16/group. Error bars are SEM.

### Vium Arthritis Index™ rank orders compound efficacy similar to histopathological assessment

Table 2: Rank ordering of therapeutic efficacy of compounds by method of arthritis assessment

Compound	Histology (score)	Vium Arthritis Index™	Δ Joint Size (in)
Vehicle	10.8 +/- 2.4	9.5 +/- 1.4	0.13 +/- 0.03
MC-105	6.3 +/- 4.1*** (1)	7.4 +/- 2.0*** (1)	0.08 +/- 0.05*** (1)
MC-103	7.9 +/- 4.5* (2)	7.9 +/- 2.5* (2)	0.11 +/- 0.06 (3)
MC-110	8.2 +/- 4.1* (3)	8.3 +/- 3.4 (4)	0.11 +/- 0.04 (3)
MC-114	8.4 +/- 4.2 (4)	8.3 +/- 2.8 (5)	0.08 +/- 0.04*** (1)
MC-104	8.9 +/- 3.6 (5)	8.4 +/- 2.1 (6)	0.11 +/- 0.04 (3)
MC-106	9.3 +/- 2.6 (6)	9.4 +/- 2.6 (8)	0.11 +/- 0.03 (3)
MC-101	9.8 +/- 3.4 (7)	9.0 +/- 2.4 (7)	0.12 +/- 0.05 (8)
MC-112	10.0 +/- 2.9 (8)	9.5 +/- 1.4 (9)	0.12 +/- 0.04 (8)
MC-111	10.3 +/- 3.9 (9)	7.9 +/- 2.1* (2)	0.11 +/- 0.04 (3)

Nine re-purposed compounds assessed at 3 doses each are ranked from most to least efficacious based on histological assessment. For the purposes of this table, doses were combined. Rank ordering based on the Vium Arthritis Index™ closely matches histology for all compounds but MC-111 (blue highlight). \**p* < 0.05 vs. vehicle, \*\*\**p* < 0.001 vs. vehicle

## Conclusion

We developed an automated, objective, function-related arthritis index to track disease and evaluate therapeutic efficacy in animal models of rheumatoid arthritis. The Vium Arthritis Index™ can:

- reproducibly track arthritis severity in response to vehicle or standard of care drugs
- better detect mild disease pathology than conventional joint measurements
- allow for better use of resources during high scale drug profiling

Our results demonstrate how a low-touch, high-tech platform can pave new ways for more rapid, reproducible, drug discovery and evaluation, not only for RA, but also more broadly in other autoimmune diseases such as MS and Lupus, as well as outside of immunology in cancer, CNS, toxicology and other areas.