Challenge 22: Osteo-chip

Launch Meeting

08 September 2016

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The Challenge

"An *in vitro* model to recapitulate the human osteoarthritic joint that will:

- Provide a device or platform capable of mimicking the human osteoarthritic joint in a physiologically relevant manner utilizing some combination of human joint tissues, fluids, and/or equivalent cell lines.
- Provide a device or platform which is amenable to use in drug discovery and development studies in OA with the potential for adaptation to modeling of both early and late stage disease, mechanism, progression, and correlation to clinical biomarkers.
- The device should be medium throughput and compatible with standard equipment and measurement platforms (e.g. microscopy, biochemical analysis, FACS, robotics). "

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Current Approaches to Arthritis Research:

A Summary of Published Studies

- Published approaches vary according to access to materials and expertise in the field.
- Understanding of osteoarthritis disease development is limited
  - Age, trauma, obesity & genetics
- Push toward personalized medicine based on disease etiology
  - Treatment: pain, function & progression

In vitro

- Cell Culture Systems
  - Immortalized cell lines, Primary human cells
- Generally 2D monocultures – no "gold standard" for 3D or multi-culture system

Ex vivo

- In situ culture of tissue pieces or tissue homogenate
- Inherently multi-culture system
  - Population selection can remove paracrine survival signals
- Lack of homeostatic signals often leads to population selection and de-differentiation
- End stage

In vivo

- Multiple animal models available
- Frequently acute/active models
- Model individual mechanisms of joint disease

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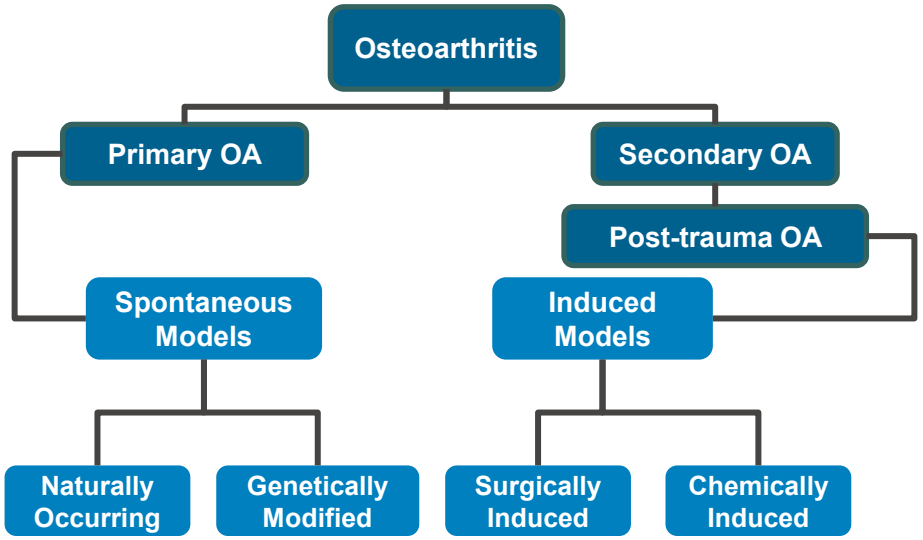
Current Approaches to Arthritis Research



Adapted from: J Orthop Surg Res. 2016; 11:19.

Rheumatoid Arthritis Models		Species	Disease Feature	Variations
Trigger-Induced Models	Non-specific Immune Stimuli	Rat	AI	3
	Cartilage-directed autoimmunity	Mouse	AI	2
	Infectious agent/exogenous triggers	Mouse/Rat/ Rabbit	AI/Flare	4
Immune Complex Models		Mouse	Innate Immune Activation	3
Transgenic Spontaneous Models		Mouse	Various	7

Adapted from: Arthritis Res Ther. 2009; 11(5): 250.

- Most commonly used models represent secondary osteoarthritis
  - Short time course to progression representative of acute disease or disease flares
  - Similar to induced models of Rheumatoid Arthritis
- Spontaneous models more representative of OA pathogenesis, but high cost associated with lengthy time to progression.
- In general, animal models depict individual mechanisms of pathology, providing a snapshot of disease rather than a representation of pathogenesis.

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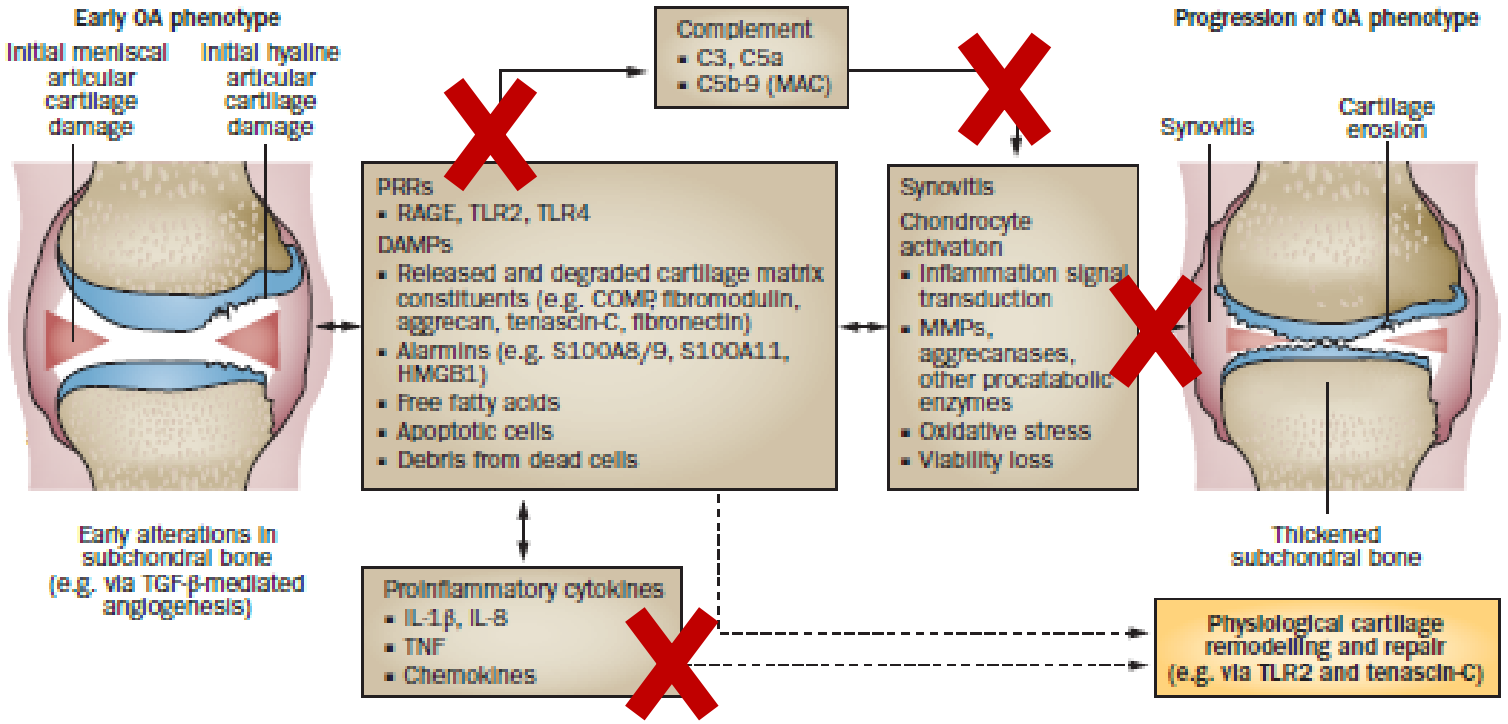
Current Approaches to Arthritis Research



From: Nat Rev Rheumatology. 2015; 11:35-44

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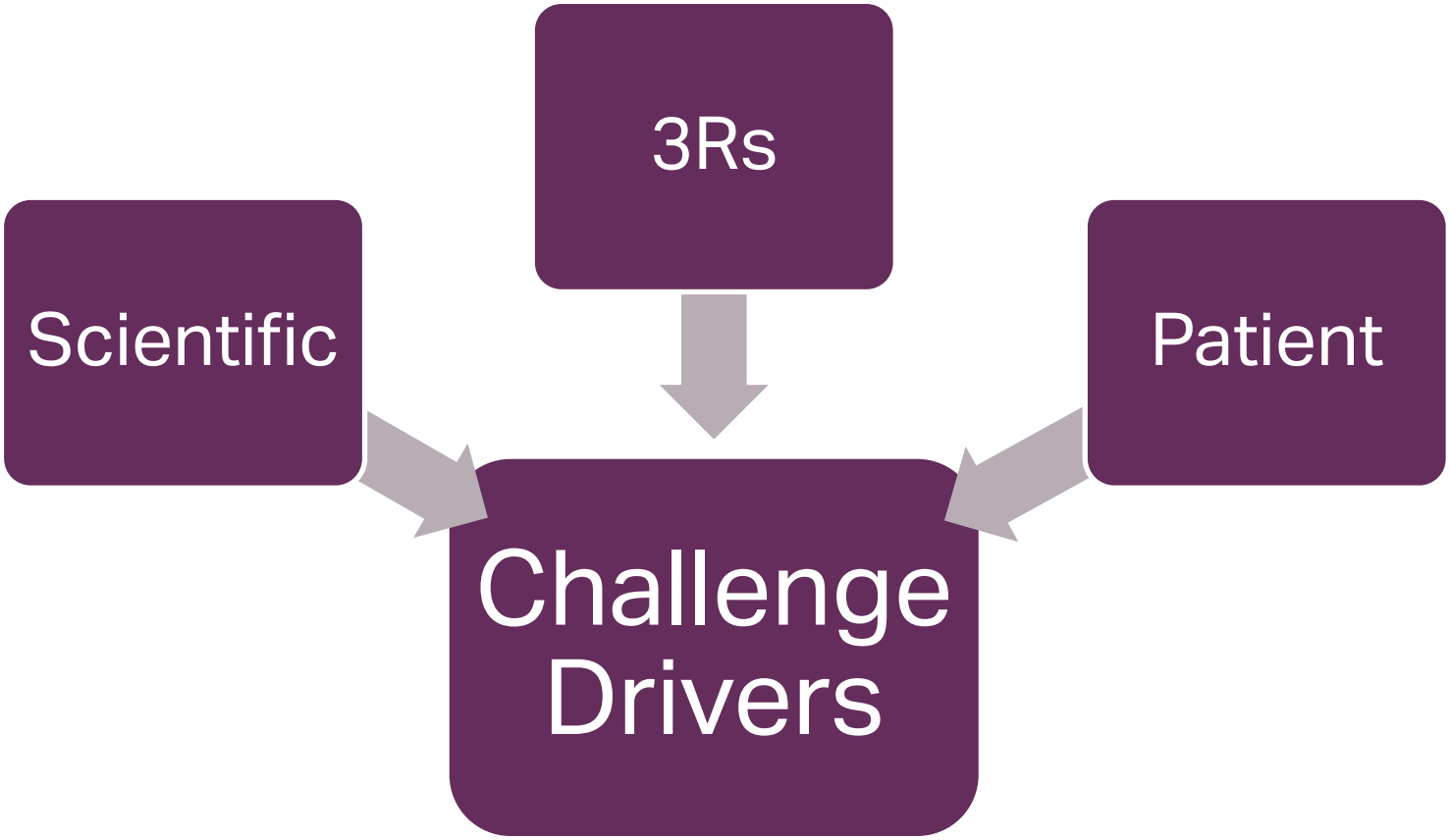
Why was this Challenge Developed?



Patient and Scientific Benefits

- Improved understanding of the driving mechanisms of disease – helping industry to pick the **right target** for the **right patient**
- Greater reliability and robustness of pre-clinical data will help move away from the “one size fits all” approach to therapy
  - Personalize treatment strategy based on disease stratification
- Better selection of appropriate animal models will improve quality of data and increase likelihood of getting the **right treatment** to the **right patient** at the **right time**.

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3Rs Benefits

Depending on nature of the “solution”

Replacement

- Exploratory studies to identify redundancy in the system can be replaced by a more holistic *in vitro* model – Right target for the right model system

Refinement

- More descriptive *in vitro* studies can fine-tune the type and timing of endpoints *in vivo*.

Reduction

- Better dose predictions *in vitro* would result in fewer study arms and reduced animal numbers.

Deliverables

This CRACK IT Challenge aims to develop an advanced in vitro model of the human osteoarthritic joint that will:

- **Reduce** the number of animals used in preclinical OA drug development and academic research by providing an alternative to the animal models.
- Improve the **predictive power** of preclinical models to humans through more extensive use of human tissues and/or cells.
- Provide a **robust** and **reliable** tool for development of potential disease modifying OA drugs.

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Deliverables

Phase 1 Deliverables

- Development of a cell culture platform that produces a mixed stable cell culture of cell types that represent the key components of the human joint. These should include:
    - Synoviocytes – type I and type II
    - Osteoblasts
    - Osteoclasts
    - Chondrocytes/cartilage or cartilage-like matrix
    - Adipocytes
    - Immune cells.
- Demonstration of cell phenotype stability and viability for at least (72 hours) as indicated by appropriate biomarkers/readouts.
- Robust plans to deliver Phase 2 of the Challenge.

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Deliverables

Phase 2 Deliverables:

Development of an in vitro human OA model that:

- Recapitulates the (3D architecture and) physiology of the OA joint.
- Provides measurable cartilage matrix and inflammatory responses as evidenced by:
  - Cartilage degradation and regeneration readouts
  - Cytokine readouts
  - Cell activation markers (e.g. immune cell phenotype).
- Provides physiological responses to stimuli and disease states that act as measures of efficacy and toxicity for new treatments (including both small molecules and biologics).
- Achieves a throughput level that permits the screening of ten candidates or more per week.

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Deliverables

Phase 2 Deliverables:

Development of an in vitro human OA model that (Continued):

- Improved biological relevance on current *in vitro* models, as evidenced through data demonstrating predictive capabilities.
- Guarantees a robust and ethical supply of source cell material.
- Provides mechanistic insight into:
  - Disease progression
  - Drug mechanism of action

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Deliverables

Phase 2 Desirables:

- The ability to model diseased and healthy states.
- A flow system containing synovial fluid or an equivalent.
- The addition of shear stresses and forces to mimic mechanical movement of the joint.
- Measures of pain (biomarkers and/or electrophysiological).

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Sponsor In-Kind Support

Phase 1:

- Intellectual input in hypotheses development and industry perspective on applicability and impact.

Phase 2:

- Expertise in OA and *in vitro* models including specifications for an *in vitro* model which is fit for purpose for drug testing in an industry setting.
- A reference training compound set.
- Reagents and appropriate controls.
- Analytical advice.
- Potential for in-house testing using the system to test transferability and reproducibility of the *in vitro* model.

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Thank You

The Sponsors are happy to discuss the challenge and potential applications with people in the run up to the submission deadline

Sponsor contacts are:

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Backup slides

Model	Abbrev	Spp	Feature	IC	T cell	Ref
Trigger-induced models						
Non-specific immune stimuli						
Adjuvant-induced arthritis	AA	Rt	AI	-	+	[1,2]
Oil-induced arthritis	OIA	Rt	AI	-	+	[3]
Pristane-induced arthritis	PIA	Rt	AI	-	+	[4,5]
Cartilage directed autoimmunity						
Collagen-induced arthritis	CIA	Mu	CII AI	+	+	[6,7]
Proteoglycan-induced arthritis	PGIA	Mu	PG AI	+	+	[8,9]
Infectious agents/exogenous triggers						
Streptococcal cell wall arthritis	SCW-A	Rt	Persistent bacteria AI	-	+	[10]
Flare	SCW-F	Mu	Th17	-	+	[11]
Antigen-induced arthritis	AIA	Rb/Mu	Persistent antigen	+	+	[12,13]
Flare	AIA-F	Mu	Th17	-	+	[14]

Model	Abbrev	Spp	Feature	IC	T cell	Ref
Transgenic spontaneous models						
HTLV-induced arthritis	HTLV	Mu	Viral tax antigen	-	+	[15]
KRN arthritis	KRN	Mu	GPI AI	+	+	[16,17]
SKG arthritis	SKG	Mu	ZAP-70 T cell defect	-	+	[18,19]
GP130 arthritis	GP130	Mu	STAT3, T cell defect	-	+	[20,21]
TNF transgenic arthritis	TNFtg	Mu	TNF overexpression	-	-	[47,48]
IL-1ra transgenic arthritis	IL-1ra-/-	Mu	Autoimmune T cells	±	+	[23]
IL-1 transgenic arthritis	IL-1tg	Mu	IL-1 overexpression	-	-	[22]
Immune complex models						
Collagen type II	CAIA	Mu	Mouse CII antibody	+	-	[26,27]
KRN serum	GPI	Mu	Mouse GPI antibody	+	-	[31]
Poly-L-lysine-lysozyme	PLL-L	Mu	Cationic antigen	+	-	[28]

Arthritis Res Ther. 2009; 11(5): 250