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The Gap Between Clinician-led Cell Therapy Evidence and Marketed Products:

A quasi-experimental comparative pilot study of young venture clinical development

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Abstract

Background: There is an enormous discrepancy between number of trials and publications for more-than-minimally manipulated (MTMM) autologous cell based therapies versus approved products, representing a significant economic investment not yet realizing value for patients. While trials led by clinicians continue to demonstrate the enormous potential benefit of cellular therapies, relatively few products have been commercialized. This research aimed to examine barriers for young firms (aged <5 years) engaged in commercial development of cell therapies.

Methods: A quasi-experimental study examined redacted clinical regulatory documentation obtained via United States (US) Freedom of Information Act and available institutional documents, including those submitted to US Food and Drug Administration (FDA) as part of pre-market application or response documents. Sixteen documents from established firms and 16 from young firms (incorporated ≤5 years) were coded by categorical agency comment type, and results were compared by Mann-Whitney test. Number of publications (PubMed indexed) and registered clinical trials (ClincialTrials.gov) were examined based on keyword searching. Further, semi-empirical field data were collected via interviews with firm members and data are presented descriptively to provide supporting field evidence of impact.

Results: A total of 26,938 cell therapy trials (8,601 active) are registered to clincialtrials.gov. Further, 42,849 cell therapy articles are indexed on PubMed, with a 10-year mean publication growth rate of 7.07% (2.35-10.95%). Oncology- and cardiology-related articles together make up more than 44% of all publications and the majority of registered trials (71.9%). Of sampled regulatory documents, issues with pre-marketing application documents most frequently included inadequate preclinical model selection, inadequate manufacturing conditions, lack of batch control, and inadequate rationale for benefit in context of care pathway were most commonly cited. Semi-empirical data revealed that lack of requirements understanding and a budget-driven waterfall approach to development among young firms often leads to additional time and prohibitive investment to complete development.

Conclusions: The immense burden placed on small firms to complete costly testing activities and limited clarity on marketing requirements places these firms at a significant disadvantage compared to large firms. This study provides initial semi-empirical evidence that can be used to improve young firm performance and inform venture investment in these firms.

Background

There is an enormous discrepancy between the number of trials and publications for more-than-minimally manipulated (MTMM) autologous cell-based therapies versus approved products, representing a significant investment that is not yet realizing value for patients. While trials led by clinicians continue to demonstrate the enormous potential benefit of cellular therapies, relatively few products have been commercially approved. This research aimed to examine barriers for young firms (aged <5 years) engaged in development of cell therapy products and potential process improvements.

The United States (US) Food and Drug Administration (FDA) Office of Tissues and Advanced Therapies (OTAT) currently lists only 18 approved cell therapy products available to US markets (FDA, 2018). Similarly, only 10 advanced therapy medicinal products (ATMPs) have been approved by EMA to date, or which 4 have been withdrawn. This has provided basis for recent changes in regulatory oversight of manufacturing (e.g., guidance for continuous manufacturing, for instance) and collaboration with experts to explore challenges associated with research and development (R&D) in relatively high cost, small population targets, with the majority of trials in the United States (Hanna *et al.* 2017).

Status of Advanced Therapies (2018)

66.8% of all **CLINICAL TRIALS** are in USA (Hanna *et al.* 2017)

18 Cell/Gene Approvals (per OTAT)

10 ATMP Approvals (4 withdrawn)

only about **3.68%** make it to **PHASE 3** (Hanna *et al.* 2017)

Image credit: Bruce Wetzel & Harry Schaefer. AV-8202-3656 1982. National Cancer Institute (Public domain)

Results

Bibliometric Analysis

In order to contextualize the gap between publication rates for MTMM cell therapies, a bibliometric analysis was conducted using a Unix-based PERL script interfacing with the BLAST URL API and Entrez Programming Utilities (E-utilities), to mine 10-year data for number of articles containing a composite of MeSH terms for MTMM cell therapies in the title or abstract of PubMed database entries (Jan 2008-Jan 2018). While this PubMed scripting may over-approximate numbers of articles, custom PERL scripting enables more sophisticated queries, duplicate elimination, and complex search logic designed to improve aggregate results. Approval data for FDA-regulated products was taken from the FDA OTAT website (FDA, 2018).

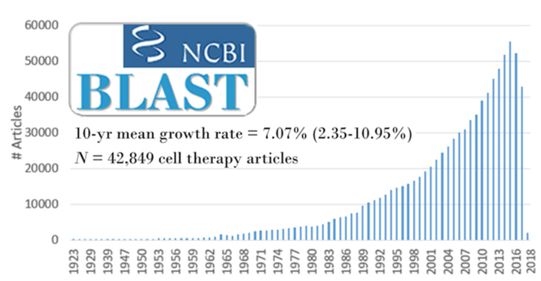


Figure 1. Number of PubMed-indexed articles addressing MTMM cell therapies

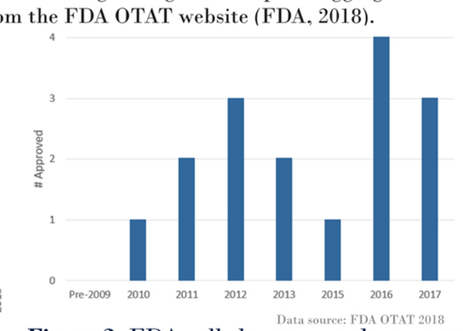


Figure 2. FDA cell therapy product approvals by year (<2009 - 2017)

Regulatory Document Analysis

A convenience sample of N = 32 regulatory documents were obtained through current or past United States (US) Freedom of Information Act requests and institutionally available documents, including pre-market correspondence, including 16 from established firms and 16 from young firms (defined as those incorporated ≤5 years).

Documents were read by a single reviewer and qualitatively coded by agency comment/deficiency topic ("type").

Two-tailed Mann-Whitney U Test showed that deficiencies were significantly more common in young firms than in established firms (U = 17, Z = 3.69879; P = 0.00022).

$$U = NM + \frac{N(N+1)}{2} - \sum \mathrm{Rank}(x_1)$$

Deficiencies are significantly more common in young firms (P = 0.00022)

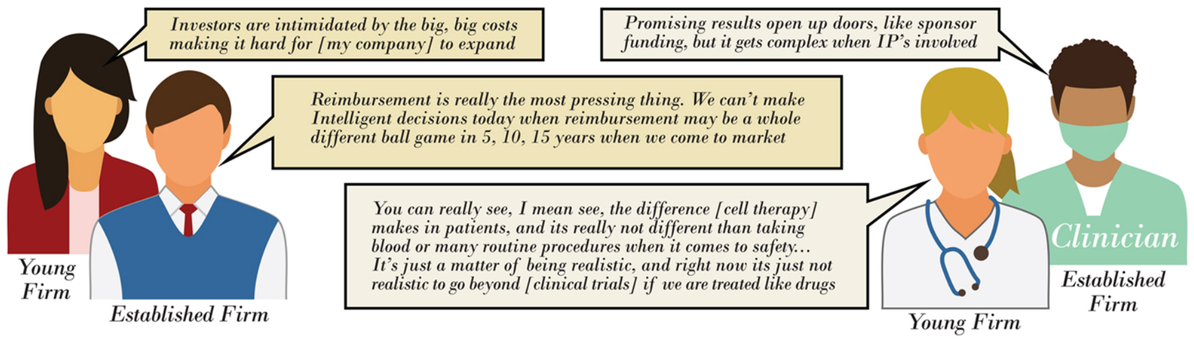
	Young Firm (incorporated <5 years)	Established Firm
Inappropriate preclinical model selection	3	0
Inadequate manufacturing conditions, lack of batch control	8	1
Inadequate indications (i.e., too broad)	2	2
Inadequate rationale for benefit in context of care pathway	5	2
Inappropriate bioavailability (BA)/bioequivalence (BE)	9	0
Failure to address product-specific risks	7	4
Materials and sourcing/manufacture issues	7	2
Missing/inappropriate preclinical testing	8	0
Missing/inappropriate sterility testing	7	0
Inconsistent nomenclature	9	3
Testing does not support indications	3	2
Population not appropriate	1	1
Missing documents	5	2
Document incorrectly submitted or formatted	3	0

Figure 3. Deficiencies noted by agency reviewers in young firm vs. established firm regulatory documents

Computed Using Social Statistics Engine 2018 (http://www.socscistatistics.com/tests/mannwhitney/Default2.aspx)

Ethnographic Field Data (Interviews)

Semi-empircal ethnographic field data were conducted with *N* = 4 anonymous interviewees via skype audio (2 clinicians and 2 industry representatives from young vs. established firms). All interviewees were senior staff employed in the USA with applicable clinical development experience of at least 8 years. Interviewees were asked about their perceptions of health policy affecting cell and advanced therapy organizations, as well as about their understanding of the gap between publications in cell therapy and marketed products. Representative quotes and constructed boundary (pathway) maps are presented.



Maps of Boundary Objects, often used in organizational communication research, can help construct pathways modeling organizational challenges

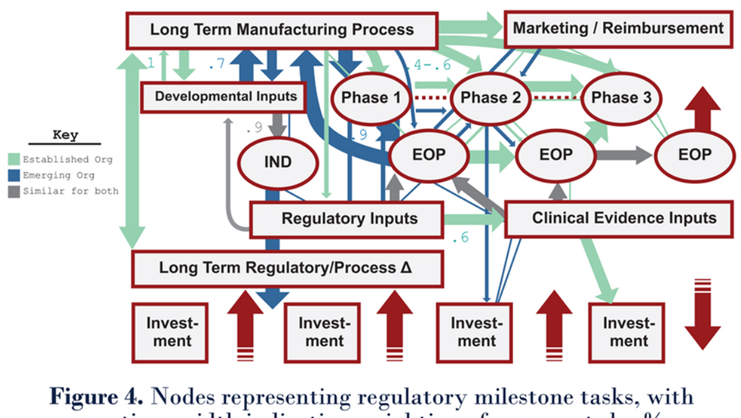


Figure 4. Nodes representing regulatory milestone tasks, with connections width indicating weighting of comments by % occurrence

Conclusions & Summary of Hypothesis-Generation for Research to Reduce Inequities for Emerging Ventures in Cell Therapy

The immense burden placed on small firms to complete costly testing activities and limited clarity on marketing requirements places these firms at a significant disadvantage compared to large firms. The evidence from the boundary mapping exercise (weighted based on % occurrence of comments during interviews) reveals distinct organizational focus differences between emerging and established organizations, most notably that manufacturing processes, investment, and early phase issues are more closely linked when discussed by interviewees in emerging firms. Comparatively, perhaps due to more established manufacturing processes and resources, established firms more commonly use existing manufacturing processes and practices to inform development programs. As such, established firms generate competitive advantage that is most notable in mid- to late phase trials to support marketing applications. This study provides initial semi-empirical evidence that can be used to improve young firm performance and inform venture investment in these firms. It must also, however, be noted that this pilot is limited by the heterogeneity of samples and lack of saturation in the interview process, and thus these results are intended primarily as a pilot for hypothesis generation for future more extensive and controlled organizational research completed as part of the author's proposed doctoral research.

Regulation is needed to equalize competitive advantage linked to manufacturing infrastructure

More research is needed to determine, specifically, where proposed regulation can equalize early investments, potentially reducing overall costs associated with development and lowering barrier to entry.

Early economic research methods (e.g. RWE studies) can reduce reimbursement uncertainty

Modern "big data" and "real world evidence (RWE)" may provide aa more accessible means for clinicans to access data that reduces uncertainty in reimbursement-- but what policies are needed to facilitate this transtition?

Regulatory education aimed at clinicians can reduce adverse impact of changes in early phase development.

Within emerging clinician-led groups, often technical considerations are more heavily weighted. Education and cross-disiplianry collaboration are needed to ensure early weighting of business and regulatory issues in translational research

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