SUMMARY STATEMENT

PROGRAM CONTACT: **(Privileged Communication)** ***Release Date:*** **06/23/2019**
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Application Number: **1 R01 GM121753-01A1**

Principal Investigators (Listed Alphabetically):

CORUZZI, GLORIA (Contact)
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Applicant Organization: NEW YORK UNIVERSITY

Review Group: **GCAT**
Genomics, Computational Biology and Technology Study Section

Meeting Date: **06/12/2019** ***RFA/PA:*** **PA19-056**
Council: **OCT 2019** ***PCC:*** **G121DA**
Requested Start: **09/01/2019**

Project Title: **Hit-and-Run transcription: The impact of transient interactions in dynamic gene regulatory networks that mediate rapid nutrient signaling**
SRG Action: **Impact Score:29 Percentile:13**
Next Steps: **Visit https://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **10-No human subjects involved**
Animal Subjects: **10-No live vertebrate animals involved for competing appl.**

Project Year	Direct Costs Requested	Estimated Total Cost
1	362,798	566,974
2	402,343	628,774
3	376,590	588,528
4	374,542	585,327
TOTAL	1,516,273	2,369,604

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

1R01GM121753-01A1 CORUZZI, Gloria

RESUME AND SUMMARY OF DISCUSSION: This application proposes to characterize transient transcription factor-target interactions using computational and experimental methods in Arabidopsis model system. Successful completion of the aims may provide deeper insights into transcriptional regulation hence the work is potentially significant. The investigators have complementary expertise, are highly collaborative and have an excellent track record of publications. Extensive preliminary data lend credence that the work will be successful. There was high enthusiasm for the large-scale investigation of the 'hit-and-run' model of transcriptional regulation and it was thought to be extensible to other model systems. Innovative methods are utilized to measure direct and indirect regulatory pathways and alternative methods are considered. Discussion of these aspects convinced the entire panel that high impact outcome will be derived from the work as proposed.

DESCRIPTION (provided by applicant): This grant exploits TIME - the 4th and largely unexplored dimension of transcription - to capture transient interactions in gene regulatory networks (GRNs) that are important, but missed, in vivo. This is because genome- scale methods to capture transcription factor (TF) target interactions favor stable binding, and reporter gene studies which detect transient TF-target interactions in seconds, miss global responses needed for GRN models. We aim to fill the time-gap in our collective knowledge of dynamic GRNs by experimentally capturing transient TF-target interactions globally using a cell-based temporal TF perturbation assay (Aims 1 &; 2), and evaluate their importance in forecasting gene expression at future time-points (Aim 3), a main goal of systems biology. We model temporal GRNs controlling nitrogen (N)-signaling in plants, but our approaches are broadly applicable. We exploit a cell-based assay for temporal TF perturbation, TARGET, which captures transient TF-target interactions genome-wide; i) by TF-mediated gene regulation even in the absence of detectable TF-binding, ii) within minutes of controlled TF nuclear entry, and iii) identifies highly transient TF-binding leading to sustained transcription by affinity-capture of de novo mRNAs. We discovered that i) a single TF can stably or transiently bind to, and induce or repress, distinct sets of targets depending on their cis-context, ii) that transient TF-targets captured only in cells control early N-responses in planta, for two master TFs in our GRNs (bZIP1 & NLP7). This genome-wide data supports a Hit-and-Run transcription model, where a TF Hit can initiate a stable transcriptional complex, including recruitment of TF partners, enabling transcription to continue after the initiating TF is no longer bound, the Run. This could allow a small number of TF molecules to rapidly affect a large number of target genes by acting catalytically. Our studies have been cited and influenced thinking of transient transcription mechanisms across yeast, stems cells, and were invoked to explain the new discovery of transient binding of Zelda/Bicoid to a reporter gene in Drosophila. Herein, we deploy experimental and computational innovations to test the pervasiveness and in vivo significance of a conceptual innovation - transient Hit-and- Run interactions in GRNs. Our experimental innovations include; i) Assays for Hit-and-Run activity across all 70 TF families in Arabidopsis, using a higher throughput version of the cell-based TARGET assay we recently published, ii) new methods to capture TF-target interactions using time-series biotin-ChIP and DamID, which leaves DNA methylation marks on transient TF-target interactions, supported by preliminary data (Aims 1 & 2). Our computational innovations include: i) ConnectTF, a platform to integrate TF-DNA binding and RNA-seq data and identify candidate Hit-and-Run TFs, and approaches to assess the in planta relevance of transient TF-target interactions in GRNs, such as ii) our newly published Network Walking method, and iii) OutPredict, a new time-based method to forecast gene expression at future time-points (Aim 3). Our experimental & computational approaches are broadly applicable and our results are relevant to environmental N-use affecting human health.

PUBLIC HEALTH RELEVANCE: This work illustrates a combined experimental and computational approach to discover gene regulatory networks in a pathway, process, or trait - applied across a range of problems in biology, agriculture and medicine. Our networks can suggest genes for targeted interventions to reduce nitrogen fertilizer use, yielding benefits for health, energy and the environment.

CRITIQUE 1

Significance: 3
Investigator(s): 1
Innovation: 3
Approach: 2
Environment: 1

Overall Impact: This proposal focuses on elucidating transient TF-target interactions that while short lived can predict the transcriptional states of target genes at later time points. This "Hit-and-Run" model of gene regulation will be explored in the context of responses to nitrogen application in the model plant Arabidopsis. Aim 1 focuses on the application of a cell-based genome wide assay called TARGET that is suitable for identifying candidate TFs with potential hit-and-run dynamics. This will be applied to a set of 150 TFs. Aim 2 focuses on validation of candidate hit-and-run TFs (up to ~20 candidates) using more sensitive techniques such as time-series ChIP, DamID, and 4tU. Aim 3 focuses on computational modeling of this data to carry out time-series forecasting of transcriptional states. The strength of this proposal is the focus on the dynamics TF regulation that happens immediately after introduction of an external signal (N signaling). Not many studies have successfully focused on the documenting such short-lived interactions, and exploring their consequences. The scaled up TARGET assay that the authors described is well suited as in initial screening tool, and the proposed more sensitive validation techniques will help to refine the understanding of TF dynamics. A shortcoming of the proposal is that it doesn't state whether the specific experimental approach can be generalized beyond plants.

1. Significance:

Strengths

- Efficacy of the TARGET method and the ability to identify hit-and-run regulation has been demonstrated in prior publications from the investigators.
- Understanding the dynamics of TF interations and their consequences is fundamental to improving our understanding of the gene regulation in general. The proposed research will provide insights into short timescale dynamics of TF regulation, an area that has been little explored at the genome wide level.

Weaknesses

2. Investigator(s):

Strengths

- Strong MPI team of senior investigators with excellent publications and track record of collaboration.
- The two PIs bring complementary expertise in experimental molecular biology and quantitative biology.

Weaknesses

- None noted

3. Innovation:

Strengths

- Large scale investigation of the hit-and-run model of transcriptional regulation has not been previously attempted. Date from the PI and other labs have demonstrated that the hit-and-run model may hold for at least some genes/stimuli, but this will be the first genome scale attempt to elucidate such regulatory dynamics.

Weaknesses

- Methodological innovation is modest; primarily scaling up of TARGET method (though this was already demonstrated in recent publication).

4. Approach:

Strengths

- The scaled up TARGET assay is suitable for screening a large number of TFs, and can be suitably coupled with more sensitive time series ChIP, DamID, and 4tU assays
- Suitable experimental design (replication and appropriate controls) is employed as well as secondary assays to validate candidate results from Aim 1. Appropriate computational and statistical methods are described for analysis of the large scale genomic data that will be generated.

Weaknesses

- The proposal does not discuss the potential for generalizability of the TARGET approach. Can it be readily utilized in other model organisms or is it restricted to plants?
- It would be useful to explore whether at least some of the TFs identified as having hit-and-run dynamics under N signaling show similar dynamics under other relevant stimul

5. Environment:

Strengths

- Excellent experimental and computational resources and strong scientific environment at NYU and NYU Courant.

Weaknesses

- None noted.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

- The proposal is responsive to prior critiques and there is a new publication showing the efficacy of the scaled up TARGET assay that is critical for Aim 1.

Applications from Foreign Organizations:

Not Applicable (No Foreign Organizations)

Select Agents:

Not Applicable (No Select Agents)

Resource Sharing Plans:

Acceptable

Authentication of Key Biological and/or Chemical Resources:

Acceptable

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2

Significance: 2
Investigator(s): 1
Innovation: 2
Approach: 3
Environment: 1

Overall Impact: This proposal tests a novel idea that many regulatory factors involved in nitrogen responses function by transiently setting off activation of target genes, without long-term association. So-called hit-and-run mechanisms have been documented for polycomb repressed genes, but their overall function in gene regulatory networks, and with regards to activation in particular, is unknown. The proposal focuses on developing a fine-level understanding of a set of such factors, identified from a root protoplast overexpression system that permits high-throughput analysis, even at the possible cost of in vivo context. The Hit and Run hypothesis is a testable conjecture that this study will be able to further elucidate using several innovative approaches, and even if the hypothesis is proven to be untrue, the studies will likely greatly further our understanding of this GRN by effective integration of multiple types of data. Through use of tagged TF in root cells, the study will help overcome the lack of quality ChIP data for Arabidopsis networks.

1. Significance:

Strengths

- This study seeks to identify the gene regulatory network involved in nitrogen utilization in the Arabidopsis root, comprising at least 150 transcription factors that are differentially expressed under nitrogen regulation. A special focus of the study is identifying so-called “Hit and Run” factors, whose direct transcriptional influence can be measured, even when physical association with target genes is lacking.
- Hit and Run function is defined as the lack of a ChIP signal; whether this truly represents a catalytic function of a TF on a gene switch is not clear; differential accessibility of ChIP epitopes or poor crosslinking of tethered TF may also underlie this phenomenon.

Weaknesses

2. Investigator(s):

Strengths

- Dr. Coruzzi is a senior and highly productive researcher in systems biology of plant gene regulatory networks, with a focus on nitrogen metabolism. Her laboratory has pioneered the use of a number of technologies that are key to mapping transcription factors and their gene targets on a genomic basis. The laboratory has also developed a computational tools for effective assessment of high throughput data. Dr. Shasha has collaborated with Dr. Coruzzi on many previous studies, contributing expertise in computational biology. Dr. Katari is a project manager for VirtualPlant, and has extensive experience in plant systems biology data management and visualization.

Weaknesses

3. Innovation:

Strengths

- This proposal combines effective and innovative methods to better discern direct and indirect regulatory pathways involved in plant nitrogen metabolism. In particular, the TARGET technology, whereby specific TF are acutely induced in root protoplasts, provides a means by which functional targets of the factors can be identified. Furthermore, methods that infer physical interactions are used to identify “hit-and-run” candidate factors. Finally, this proposal combines cell-based perturbation analysis with in planta data to computationally infer direct and indirect GRN relevant to the intact organism.

Weaknesses

4. Approach:

Strengths

- This proposal tackles the systems-level analysis of nitrogen regulation using complementary technologies, each with limitations and advantages, but on the whole well-balanced to generate important advances in this field. Alternative approaches are suggested in case primary lines of attack hit blocks. The analysis of sets of genes with potential hit-and-run function ensures that general trends can be identified, if they exist.
- Scaling up from a recent project examining 33 TF with roles in root response to nitrogen, in a first Aim, 150 TF (apparently those found to change in expression during nitrogen stimulation) will be assessed by TARGET technology, whereby DEX inducible forms of the proteins will be activated in transfected root protoplasts to regulate transcription. The experiments are conducted in the presence of cycloheximide to block secondary effects.
- The TARGET system allows a much higher throughput analysis of TF than whole plant assays, and permits direct target assessment by finer kinetics and use of CHX.
- TF occupancy will be assessed by ChIP, using a BirA biotinylation peptide tag.
- Factors found to regulate many genes with little or no binding will be identified as “Hit-and-Run” candidates.
- In a second aim, ~20 of these Hit and Run factors will be further studied using ChIP in a time series, 4thioU to label nascent transcripts, and DAM-ID to methylate regions of the genome transiently contacted by TF.
- Preliminary DAM-ID data from the NLP7 TF shows effectiveness of this approach.

- The same candidate Hit and Run TF will be fused to an estrogen-inducible cassette to permit induction in transgenic plants, and RNA-seq will be employed to judge responses to plants overexpressing the TF with or without nitrogen stimulation.
- Computational analysis of cellular and in planta responses will be integrated in a third aim to predict direct and indirect regulatory interactions, developing a GRN for nitrogen regulation.

Weaknesses

- The TARGET system uses protoplasts of root cells of multiple lineages, thus transcriptional function is a composite of an overexpressed TF in different settings.
- A transcriptional signal from one cell type may not match low ChIP occupancy from bulk roots cells, thus generating false Hit and Run signals.
- Assays rely entirely upon overexpression to identify regulatory circuits.
- 150 TF selected were apparently those whose transcript levels change during nitrogen signaling, leaving out possibly important TF whose mRNA levels do not change.

5. Environment:

Strengths

- The NYU Center for Genomics and Systems Biology is a highly appropriate setting for the proposed research, and recent publications have shown the effectiveness of current nitrogen systems biology investigation.

Weaknesses

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

- In the first round of review, several reviewers questioned what one gained from partitioning TF into Hit and Run and non-Hit and Run candidates. From the description provided here, it appears that including genes that may be direct physical targets, but not identified as such, can improve the assembly of an accurate GRN. A question about 4tU and DAM-ID suitability is answered by preliminary results shown in this proposal.

Applications from Foreign Organizations:

Not Applicable (No Foreign Organizations)

Select Agents:

Not Applicable (No Select Agents)

Resource Sharing Plans:

Acceptable

Authentication of Key Biological and/or Chemical Resources:

Acceptable

Budget and Period of Support:

Recommend as Requested

CRITIQUE 3

Significance: 3
Investigator(s): 1
Innovation: 2
Approach: 4
Environment: 1

Overall Impact: This proposal focuses on the “hit and run” model of TF action, in which a small set of TFs transiently binds and recruits other TFs for sustained transcription after the “pioneer” TF leaves. This model, initially proposed in the late 80ies, has since been supported by the PI’s prior published work and several studies by other authors. The “hit and run” mode of TF action is thought to facilitate fast environmental and developmental responses.

Substantial prior method development together with extensive preliminary data establish the feasibility of this conceptually and methodologically ambitious project; however, the extent of published data on TF function in nitrogen signaling (33 known N-responsive TFs were investigated in a 2019 study) dampens enthusiasm as gains in explanatory power for this proposal (investigation of 150 TFs proposed, 99 involved in N-signaling) may show diminishing returns. Nevertheless, the proposal addresses timely questions and challenges in the field – genome-wide studies of chromatin accessibility and ChIP-seq for individual TFs have found only weak correlations between changes in chromatin accessibility/ TF binding and changes in neighboring gene expression. It also remains unclear how certain environmental signals are extremely rapidly translated into increased gene expression at many distinct but dispersed specific loci in the genome – invoking “hit and run” TFs provides an attractive model for signal amplification.

The rigorous differentiation between directly regulated and bound TF targets, combined with methods for detecting transient interactions and *de novo* transcription, represents an impressive tour de force that will certainly yield insights into TF site recognition and regulation of gene expression. In fact, its scope (150 TFs) may reject that the PIs’ hypothesis that “hit and run” TFs are ‘master’ or ‘pioneer’ TFs if a majority of the probed TFs appear to scan the genome for possible binding sites.

1. Significance:

Strengths

- The concept of hit and run TFs is supported by extensive published data, both by the PI’s and other investigators.
- Gene regulation has become only more challenging to understand and predict in the era of genome-wide data sets for chromatin accessibility, histone modifications, and ChIP-seq and Y1H data for many important TFs. Dynamic ChIP-or accessibility peaks are weak indicators of changes in nearby gene expression; even deletions of regulatory sites do not affect gene

expression in many instances, suggestive of regulatory complexity. The concept of “hit and run” TFs resolves the conundrum of TF-regulated genes (altered expression) which were TF-unbound by bulk ChIP-seq.

- The TARGET system rigorously distinguished between direct TF targets and indirect ones. Although “bound vs. unbound” relies on failure to detect ChIP-signal, this is complemented with a method to detect transient interactions (DamID).
- The PIs have extensive expertise in the suggested experimental and analytical procedures, several of which they pioneered.

Weaknesses

- The extent of preliminary (and published) data presented diminishes the significance and impact of the proposed work somewhat. In their 2019 study, the PIs validate ~77,000 TF-target edges for 33 TFs that control 88% of all genes that are nitrogen-responsive. Does the resulting GRN allow predictions about the consequences of individual TF knockouts/ deletions of regulatory sites? How much predictive knowledge will we gain if we understand the control of 90% of genes or 95%?
- Could a different stimulus be used to venture beyond N-signaling? Drought? Pathogens?
- The “hit and run” paradigm can explain gene expression in the absence of TF binding. However, pervasive TF binding (transient or stable) as evidenced by ChIP, DamID, calling card approaches (transposon insertion) or chromatin accessibility and absence of altered gene expression appears to be the larger phenomenon. TF-bound regulatory sites are often poised for activation in response to environmental signals – this type of regulation is not captured here and neither is release of repression (as GR-TFs enter nucleus upon release from Hsp90).
- Both DamID and ChIP suffer from specificity issues (as noted by the PIs and addressed with time series and replicates).

2. Investigator(s):

Strengths

- The PI has an outstanding track record; the team has published much of the prior work underlying this proposal.

Weaknesses

- None noted.

3. Innovation:

Strengths

- This proposal relies on much prior technology development (TARGET, Network Walking etc) which enables in-depth and rigorous characterization of TF function at genome-scale. Recent genome-scale technologies such as DamID and 4tU are combined in innovative ways with classic transgenic approaches.

Weaknesses

- The continued focus on nitrogen-signaling diminishes novelty and potential for generalization to other GRNs.

4. Approach:

Strengths

- Extensive preliminary data support the feasibility of the proposed experiments and analyses.

- Validations with transgenic plants test whole organism significance.
- This is a well-crafted and well-though-out proposal.

Weaknesses

- The PI explains in the Introduction to resubmission why the proposal scales up to 150 TFs representing all 70 TF families in *A. thaliana* rather than focusing on the mechanisms and timing etc. of hit and run transcription. Nevertheless, this scale-up approach is somewhat unsatisfying – invoking as many as 20 new 'hit and run' TFs in nitrogen signaling seems contrary to the concept of a few "master or response-pioneer" TFs. Probing fewer representatives of all TF families (possibly just focusing on the most ancient member of each TF family) across several perturbations may identify shared and divergent sets of "hit and run" TFs and thereby provide stronger support for the tested concept.
- It is mentioned in several places that induced transcription levels between transient sites and stable TF-bound sites do not differ. If so, why are some sites bound transiently and others stably? Are there any distinguishing features such a chromatin marks, proximity to other genomic features etc.? Why bother to hit and run?
- If hit and run is interpreted as a solution to signal amplification – would testing different protein levels of the previously characterized "hit and run" TFs alter the results? The fusion proteins are expressed under the control of a strong viral promoter – does this extreme overexpression play a role in promoting transient probing of the genome for binding sites? Are transient and /or stable binding sites enriched in chromatin-accessible regions (ATAC data is available for Arabidopsis roots)?
- As an aside, GR is a well-known hit and run TF in mammals – does the use of GR in the fusion proteins facilitate their hit and run propensities?
- The described data from the Target system are based on bulk assessments of expression and methylation. Although transfected cells are sorted, heterogeneity in DEX uptake, DEX-induction of fusion protein transport and ensuing differences in regulation may obscure some of the relationship between TF binding and gene expression. Such heterogeneity may be resolved at the single cell level through combined analysis of gene expression and chromatin accessibility (which would also address poised regulatory sites) in single cells.

5. Environment:

Strengths

- Excellent research environment.

Weaknesses

- None noted

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Acceptable

Applications from Foreign Organizations:

Not Applicable (No Foreign Organizations)

Select Agents:

Acceptable

Resource Sharing Plans:

Acceptable

Authentication of Key Biological and/or Chemical Resources:

Acceptable

Budget and Period of Support:

Recommend as Requested

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

Footnotes for 1 R01 GM121753-01A1; PI Name: CORUZZI, Gloria

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

Genomics, Computational Biology and Technology Study Section
Genes, Genomes, and Genetics Integrated Review Group
CENTER FOR SCIENTIFIC REVIEW
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06/12/2019 - 06/13/2019

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* Temporary Member. For grant applications, temporary members may participate in the entire meeting or may review only selected applications as needed.

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