ABSTRACT FACE PAGE

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9. **Presenting Author's Career stage: (check one)**
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10. **Website / twitter handle / other public links (optional): _____**
11. **Is this the research presented in this abstract supported by IMAG MSM-related U01 funding? Yes or No**
12. **If the Presenting Author is a trainee, who is the trainee's primary research advisor? _____Prof. Aleksander S. Popel from Johns Hopkins University_____**

TRAINEE POSTER AND ORAL PRESENTATION COMPETITONS:

New to the meeting this year, we are holding *both* a trainee poster competition and a trainee oral presentation competition! If the presenting author is a trainee (i.e., a student at any level or a post doctoral trainee), he/she may enter his/her abstract in the trainee poster competition, the trainee oral presentation competition, or both competitions. Trainees may also submit more than one abstract to the meeting and enter more than one abstract in these competitions. Prizes will be given to the presenters of the top-ranked trainee oral presentation and the top-ranked trainee poster (judged during the meeting by the Program Committee).

13. **If the Presenting author is a trainee, would the Presenting Author like to enter his/her abstract in the Trainee Poster Competition*? Yes or No**

*Note: Trainees who enter the poster competition are expected to stand by their poster during the scheduled poster sessions and present them to the judges.

14. **If the Presenting author is a trainee, would the Presenting Author like to enter his/her abstract in the Trainee Oral Presentation Competition**? Yes or No**

**Note: The Program Committee will select the top four abstracts from trainees who elect to enter their abstract into the trainee oral presentation competition, these four trainees will be notified by Feb. 17th, and they will deliver their oral presentations (which will be judged) on the second day of the meeting after lunch.

USING SYSTEMS BIOLOGY APPROACHES TO INVESTIGATE THERAPEUTIC MACROPHAGE POLARIZATION IN HUMAN DISEASES

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BACKGROUND: Macrophages respond to signals in the microenvironment by changing their functional phenotypes, a process known as polarization. Depending on the context, they acquire different patterns of transcriptional activation, cytokine expression and cellular metabolism which collectively constitute a continuous spectrum of phenotypes, of which the two extremes are denoted as classical (M1) and alternative (M2) activation. To quantitatively decode the underlying principles governing macrophage phenotypic polarization and thereby harness its therapeutic potential in human diseases, a systems-level approach is needed given the multitude of signaling pathways and intracellular regulation involved.

METHODS: Here we develop the first set of mechanism-based, multi-pathway computational models (Fig. 1) that quantitatively describe the integrated signal transduction and macrophage programming under various M1, M2 (IL-1β, TNFα, IFN-γ, IL-4, IL-10, VEGFA) and cell stress (hypoxia) stimulation, using a two-step approach. The overall processes of model formulation, calibration, simulation and analyses were implemented using the MATLAB SimBiology Toolbox (MathWorks, Natick, MA).

RESULTS: The step-1 model (Fig. 1A) consisting of three major pathways was formulated to reproduce experimental time-course observations relating to different macrophage phenotype perturbations (e.g. 70+ datasets), and it has suggested novel insights regarding the hierarchical and temporal control of M1-M2 features through an integrative analysis of direct cytokine signaling, hypoxic response, transcriptional and post-transcriptional regulation, and autocrine feedbacks[1]. Using the step-1 model as a basis, we are currently finalizing our step-2 model (Fig. 1B) which includes 4 additional pathways and is calibrated against 150+ sets of quantitative experimental data derived from macrophages, plus original data obtained specifically for this project from our collaborators at Augusta University.

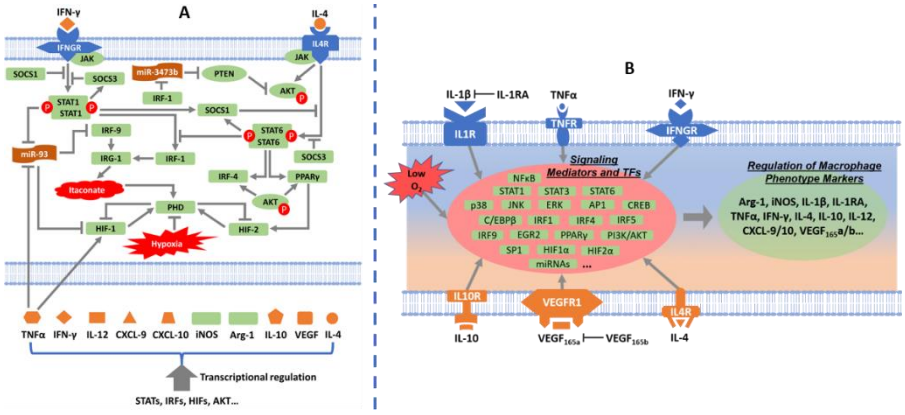

Figure 1: Schematic overview of the (A) step-1 and (B) step-2 computational models that were developed to characterize macrophage polarization at the systems-level.

CONCLUSIONS: Our computational models were calibrated extensively against experimental data, and by using these models we mechanistically elucidated a number of signature feedbacks behind the M1-M2 antagonism and investigated the dynamical shaping of macrophage phenotypes spanning the M1-M2 spectrum. Model sensitivity analysis also revealed key molecular nodes and interactions as targets with potential therapeutic values for the pathophysiology of peripheral arterial disease and cancer. In addition, we have also designed and implemented computational strategies that further incorporated our cell-level macrophage models into mechanistic tissue-level models of ischemia as well as patient-level immuno-oncology simulation platforms. In summary, through simulations that dynamically capture the signal integration and phenotypic marker expression in the differential macrophage polarization responses, we believe that our data-driven models can provide an important computational basis toward a more quantitative and network-centric understanding of the complex physiology and versatile functions of macrophages in human diseases.

REFERENCES:

1. Zhao et al. *PLoS Computational Biology*. 15(11): e1007468, 2019.

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