

**Ingenuity Pathways Analysis (IPA): Canonical pathways**

| <b>A. INITIAL ANALYSIS BY DEGs in LS versus Normal "UP"</b>                    |  | LS vs Normal UP | LS vs Normal DOWN | pre-NL vs Normal UP | PRE-NL vs Normal DOWN | post-NL vs Normal UP | post-NL vs Normal DOWN | TOTAL # GENES IN PATHWAY |
|--|--|-----------------|-------------------|---------------------|-----------------------|----------------------|------------------------|--------------------------|
| Acute Phase Response Signaling   |  | 13 (8)          | 44 (27)           | 1 (0.6)             | 18 (11)               |                      | 6 (4)                  | 164                      |
| Amyloid Processing   |  | 6 (11)          | 16 (29)           |                     | 6 (11)                |                      |                        | 56                       |
| IL-17 Signaling  |  | 7 (9)           | 22 (30)           |                     | 8 (11)                |                      |                        | 74                       |
| IL-6 Signaling   |  | 8 (9)           | 25 (28)           |                     | 9 (10)                |                      | 3 (3)                  | 90                       |
| Ovarian Cancer Signaling   |  | 11 (11)         | 31 (30)           |                     | 9 (9)                 |                      |                        | 102                      |
| Role of NANOG in Mammalian Embryonic Stem Cell Pluripotency                    |  | 11 (11)         | 27 (27)           |                     | 12 (12)               |                      |                        | 100                      |
| Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis      |  | 18 (10)         | 48 (26)           |                     | 22 (12)               |                      | 6 (3)                  | 188                      |
| Wnt/ $\beta$ -catenin Signaling  |  | 15 (11)         | 39 (28)           |                     | 11 (8)                |                      | 5 (4)                  | 140                      |
| Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis |  | 24 (14)         | 63 (37)           | 1 (0.6)             | 29 (17)               |                      |                        | 171                      |

  

| <b>B. INITIAL ANALYSIS BY DEGs LS vs pre-NL "DOWN"</b>   |           | LS vs pre-NL DOWN | LS vs pre-NL UP | LS vs Normal UP | LS vs Normal DOWN | pre-NL vs Normal UP | PRE-NL vs Normal DOWN | post-NL vs Normal UP | post-NL vs Normal DOWN | TOTAL # GENES IN PATHWAY |
|--|-----------|-------------------|-----------------|-----------------|-------------------|---------------------|-----------------------|----------------------|------------------------|--------------------------|
| Cleavage and Polyadenylation of Pre-mRNA                 | 5 (42)    |                   |                 |                 | 9 (75)            |                     | 2 (17)                |                      |                        | 12                       |
| Mechanisms of Viral Exit from Host Cells                 | 13 (29.5) |                   |                 | 4 (9)           | 16 (36)           |                     | 5 (11)                |                      |                        | 44                       |
| EGF Signaling  | 14 (29)   |                   |                 |                 | 21 (43)           |                     | 8 (16)                |                      |                        | 49                       |
| Oxidative Phosphorylation                                | 44 (26.7) |                   |                 |                 | 69 (42)           | 1 (0.6)             |                       |                      | 9 (5)                  | 166                      |
| DNA Methylation and Transcriptional Repression Signaling | 6 (26)    |                   |                 |                 | 11 (48)           |                     |                       |                      |                        | 23                       |
| NRF2-mediated Oxidative Stress Response                  | 44 (24)   |                   |                 |                 | 73 (40)           |                     | 23 (13)               |                      |                        | 183                      |
| Protein Ubiquitination Pathway                           | 48 (24)   |                   |                 |                 | 92 (46)           |                     | 33 (16)               |                      | 13 (7)                 | 201                      |
| Mitochondrial Dysfunction                                | 41 (23.7) |                   |                 |                 | 59 (35)           |                     |                       |                      |                        | 171                      |
| Clathrin-mediated Endocytosis Signaling                  | 39 (23.4) |                   |                 |                 | 58 (35)           |                     | 20 (12)               |                      |                        | 167                      |
| CNTF Signaling   | 12 (23)   |                   |                 |                 | 19 (37)           |                     | 7 (14)                |                      |                        | 52                       |
| VEGF Signaling   | 22 (23)   |                   |                 |                 | 36 (37)           |                     | 12 (12)               |                      |                        | 97                       |
| EIF2 Signaling   | 22 (22)   |                   |                 |                 | 44 (44)           |                     | 16 (16)               |                      |                        | 100                      |
| FAK Signaling  | 22 (22)   |                   |                 |                 | 33 (34)           |                     | 10 (10)               |                      |                        | 98                       |
| RAN Signaling  | 5 (22)    |                   |                 |                 | 10 (44)           |                     | 3 (13)                |                      |                        | 23                       |
| IL-9 Signaling   | 8 (22)    |                   |                 | 2 (5)           | 9 (24)            | 1 (3)               | 3 (8)                 |                      |                        | 37                       |
| IGF-1 Signaling  | 21 (21)   |                   |                 | 5 (5)           | 35 (35)           |                     | 15 (15)               |                      |                        | 100                      |
| GM-CSF Signaling   | 14 (21)   | 1 (1.5)           |                 | 4 (6)           | 24 (36)           |                     | 9 (13)                |                      |                        | 67                       |
| Docosahexaenoic Acid (DHA) Signaling                     | 10 (21)   | 1 (2)             |                 |                 | 15 (31)           |                     | 6 (12.5)              |                      |                        | 48                       |
| IL-3 Signaling   | 15 (21)   |                   |                 | 4 (6)           | 23 (32)           | 1 (1)               | 9 (12.5)              |                      |                        | 72                       |
| IL-2 Signaling   | 12 (21)   |                   |                 | 3 (5)           | 20 (35)           |                     | 8 (14)                |                      |                        | 58                       |
| JAK/Stat Signaling                                       | 13 (20)   |                   |                 |                 | 22 (34)           |                     | 8 (12.5)              |                      |                        | 64                       |
| Virus Entry via Endocytic Pathways                       | 19 (20)   |                   |                 |                 | 31 (32)           |                     | 12 (12.5)             |                      |                        | 96                       |
| PDGF Signaling   | 15 (20)   |                   |                 |                 | 27 (36)           |                     | 11 (15)               |                      |                        | 76                       |
| TR/RXR Activation  | 19 (20)   |                   |                 |                 | 27 (28)           | 2 (2)               | 11 (11)               | 1 (1)                |                        | 97                       |