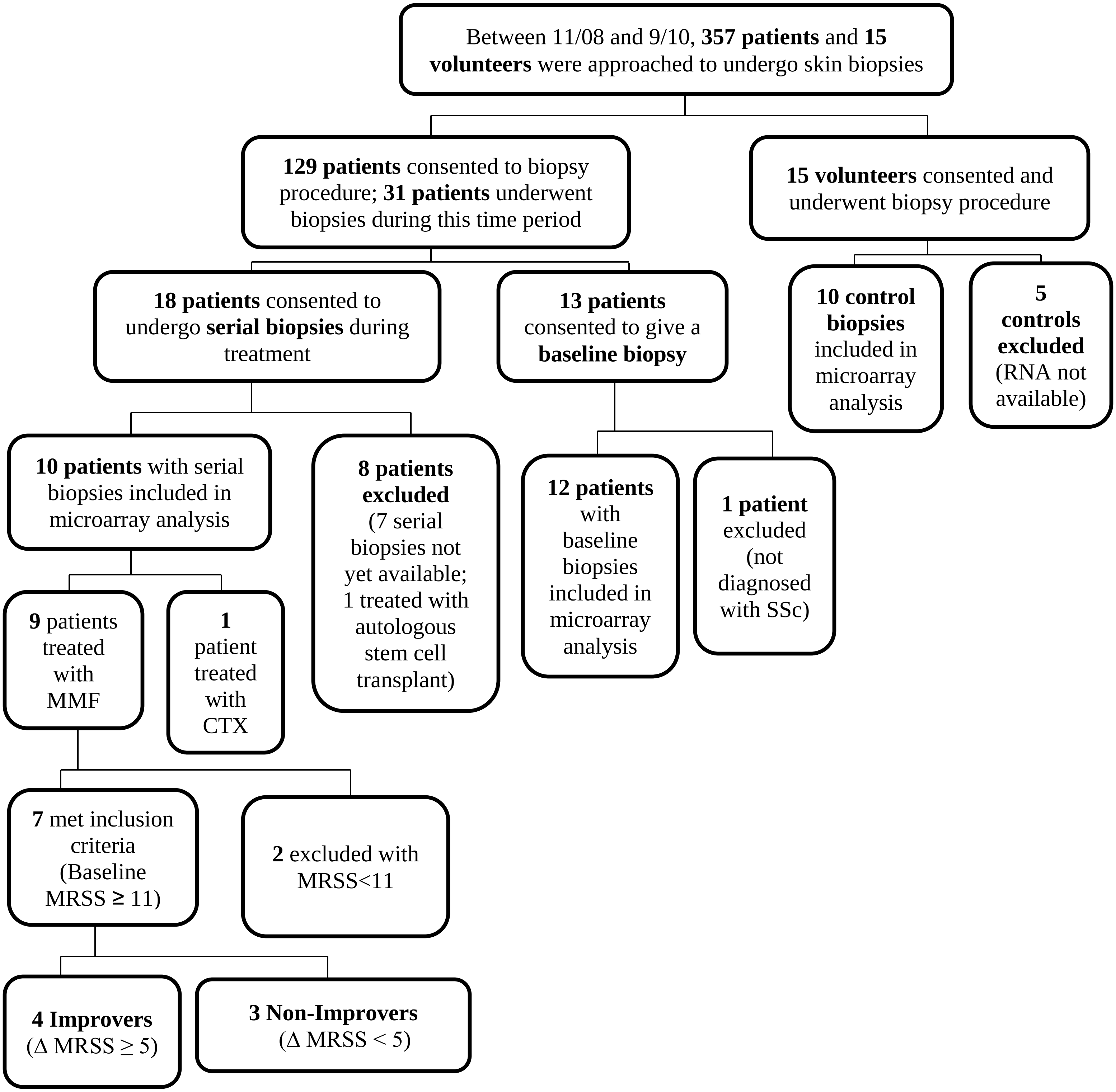
**Figure 4: Gene expression changes during MMF treatment between improvers and non-improvers.** 571 genes showed changes in expression during MMF treatment (FDR<10%). Patients that were classified as non-improvers show low levels expression of these genes, which either do not change expression or show increased expression.

**Figure 5. Validation of biologically relevant microarray findings using quantitative reverse transcription polymerase chain reactions immunofluorescence.** Results are the relative expression values normalized to the mean expression in arm samples of control subjects, $^{*}p<0.05$.

**Supplementary Figure 1:** Study cohort recruitment.



**Supplementary Figure 1**: Study cohort recruitment

**Supplementary Table 1.** Subjects and Biopsy Time Points

| Study Code | Time point | Age/Sex | Ethnicity | Skin biopsy site | Disease duration | MRSS | Disease modifying therapies |
|---|---|---|---|---|---|---|---|
| Norm01 | Baseline | 37/F | Caucasian | Left arm, Left back | | | |
| Norm02 | Baseline | 57/F | Caucasian | Left arm, Right back | | | |
| Norm03 | Baseline | 33/F | Asian | Right Arm, Right back | | | |
| Norm04 | Baseline | 37/F | Caucasian | Right Arm, Right back | | | |
| Norm05 | Baseline | 37/F | Asian | Left arm, Left back | | | |
| Norm06 | Baseline | 32/F | Caucasian | Left arm, Left back | | | |
| Norm07 | Baseline | 63/M | Caucasian | Left arm, Left back | | | |
| Norm08 | Baseline | 37/M | Caucasian | Left arm, Left back | | | |
| Norm09 | Baseline | 30/F | Caucasian/ Asian | Right arm, Right back | | | |
| Norm10 | Baseline | 33/M | Asian | Left arm | | | |
| SSc02 | Baseline | 46/F | Caucasian | Left arm, Left back | 52 | 35 | No treatment |
| SSc03 | Baseline | 48/F | Asian | Left arm, Left back | 8 | 21 | No treatment |
| | 6 month | 49/F | | Left arm, Left back | 14 | 21 | MMF |
| | 12 month | 49/F | | Left arm, Left back | 20 | 8 | MMF |
| SSc04 | Baseline | 45/F | Caucasian | Left arm, Left back | 3 | 9 | No treatment |
| | 6 month | 45/F | | Left arm, Left back | 9 | 3 | MMF |
| | 12 month | 46/F | | Left arm. Left back | 16 | 3 | No treatment |
| SSc05 | Baseline | 40/F | Hispanic | Right arm. Right back | 22 | 32 | Minocycline |
| | 6 month | 41/F | | Right arm, Right back | 28 | 21 | MMF, Minocycline, |
| SSc06 | Baseline | 54/F | Caucasian | Right arm, Right back | 16 | 16 | No treatment |
| | 6 month | 55/F | | Right arm, Right back | 22 | 11 | MMF |
| | 12 month | 55/F | | Right arm, Right back | 28 | 11 | MMF |
| SSc07 | Baseline | 60/F | Caucasian | Left arm, Left back | 112 | 4 | No treatment |
| | 6 month | 60/F | | Left arm, Left back | 119 | 4 | MMF |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 12 month | 61/F | | Left arm, Left back | 125 | 3 | MMF |
| SSc08 | Baseline | 65/F | Caucasian | Left arm, Left back | 5 | 12 | No treatment |
| | 6 month | 66/F | | Left arm, Left back | 14 | 9 | MMF |
| SSc10 | Baseline | 52/F | Caucasian | Left arm, Left back | 12 | 13 | No Treatment |
| | 6 month | 53/F | | Left arm, Left back | 18 | 13 | MMF |
| | 12 month | 53/F | | Left arm, Left back | 24 | 7 | MMF |
| SSc12 | Baseline | 51/F | Black | Left arm, Right back | 11 | 14 | No treatment |
| | 6 month | 52/F | | Left arm, Right back | 18 | 17 | MMF |
| SSc14 | Baseline | 35/F | Caucasian | Left arm, Left back | 15 | 10 | No treatment |
| | 6 month | 36/F | | Left arm, Left back | 21 | 16 | CTX |
| SSc16 | Baseline | 51/F | Caucasian | Left arm, Left back | 122 | 14 | No treatment |
| | 6 month | 51/F | | Left arm, Left back | 128 | 20 | MMF |
| SScReg1002 | Baseline | 34/F | Black | Left arm | 26 | 32 | No treatment |
| SScReg1004 | Baseline | 27/F | Hispanic | Left arm | 111 | 26 | No treatment |
| SScReg1066 | Baseline | 21/M | Black | Left arm | 22 | 15 | MTX |
| SScReg1067 | Baseline | 56/F | Caucasian | Left arm | 37 | 34 | MMF |
| SScReg1080 | Baseline | 55/F | Caucasian | Left arm | 8 | 19 | No treatment |
| SScReg1096 | Baseline | 26/F | Hispanic | Left arm | 151 | 5 | No treatment |
| SScReg1103 | Baseline | 54/F | Caucasian | Left arm | 144 | 13 | No treatment |
| SScReg1156 | Baseline | 48/F | Caucasian | Left arm | 8 | 20 | MMF |
| SScReg1213 | Baseline | 30/F | Hispanic | Left arm, Left back | 51 | 4 | No treatment |
| SScReg1269 | Baseline | 50/F | Black | Left arm | 9 | 14 | No treatment |
| SScReg1001 | Baseline | 37/F | Caucasian | Left arm | 15 | 16 | MTX |

Norm=healthy control, SSc=systemic sclerosis, SScReg=patient enrolled in the Northwestern Scleroderma Program Patient Registry, M=male, F=female, MRSS=modified Rodnan skin score, MMF=mycophenolate mofetil, CTX=cyclophosphamide, MTX=methotrexate. Disease duration=months between biopsy date and onset of first non-Raynaud symptom.

**Supplementary Table 2.** qPCR Primers for Microarray Validation

| | |
|---|---|
| CTGF | Forward: 5’-AGCTGACCTGGAAGAGAACATTAAG-3’ |
| | Reverse: 5’-GATAGGCTTGGAGATTTTGGGAGTA-3’ |
| IL-6 | Forward: 5’-AAATTCGGTACATCCTCGACGG-3’ |
| | Reverse: 5’-GGAAGGTTCAGGTTGTTTTCTGC-3’ |
| TSP-1 | Forward: 5'-TGTTTGTGCAGGAAGACAGG-3' |
| | Reverse: 5'-TTGTCAAGGGTGAGGAGGAC-3' |

qPCR was used to validate pre- and post-treatment microarray values.

**Supplementary Table 3.** Baseline Echo, PFT, and HRCT Characteristics for Subjects Newly Prescribed MMF.

| | Improvers during MMF<br>N = 4 or as indicated | Non-improvers during MMF<br>N = 3 or as indicated |
|---|---|---|
| **Echocardiography** | Mean, SD or as indicated | |
| LVEF (%) | 62, 2 | 66, 3 |
| LV mass (g/m$^2$) | 80, 14 (N = 3) | 76, 13 |
| TAPSE (cm) | 2.6, 0.4 | 2.2, 0.7 |
| RV FAC | 0.47, 0.02 | 0.50, 0.02 |
| PASP (mm Hg) | 25, 4 | 35, 6 (N = 2) |
| LV diastolic function, N (%) | | |
| Normal | 1 (33) | 1 (25) |
| Abnormal | 2 (67) | 2 (50) |
| Indeterminate | 0 (0) | 1 (25) |
| **Pulmonary Function Test** | | |
| FVC % Predicted | 88, 20 | 71, 6 |
| FEV1 % Predicted | 92, 21 | 71, 12 |
| FEV1/FVC % Predicted | 84, 5 | 80, 9 |
| TLC % Predicted | 93, 12 | 79, 6 |
| DLCO % Predicted | 75, 24 | 57, 4 |
| **HRCT Exam** | | |
| Total lung disease score | 5.75, 0.96 | 11.33, 5.03 (N = 2) |

Echo=2-dimensional echocardiography with tissue Doppler, PFT=pulmonary function test, HRCT=high-resolution computed tomography of the chest, MMF=mycophenolate mofetil, MRSS=modified Rodnan skin score, LVEF=left ventricular ejection fraction, LV=left ventricle, TAPSE=tricuspid annular plane systolic excursion, RV FAC=right ventricular fractional area change, PASP=pulmonary artery systolic pressure, FVC=forced vital capacity, FEV1=forced expiratory volume in one second, TLC=total lung capacity, DLCO=diffusing capacity for carbon monoxide.  Total lung disease score=5 lung lobes scored: 0=No disease, 1=0-5 (minimal disease but not normal), 2=5-25, 3=26-50, 4=51-75, 5=76-100% involvement.

**Supplementary Table 4.** Association Between Baseline Clinical Data and Improvement in Skin Score During Study Independent of Treatment.

| | Clinical improvement during study N = 7 or as indicated | No clinical improvement during study N = 7 or as indicated |
|---|---|---|
| | Mean, SD or as indicated | |
| Age | 49, 5 | 46, 16 |
| Sex, N (%) female | 7 (100) | 6 (86) |
| Race, N (%) white | 5 (71) | 4 (57) |
| SSc subtype, N (%) diffuse | 7 (100) | 7 (100) |
| MRSS | 24, 9 | 16, 5 |
| Raynaud disease duration (mo) | 19, 18 | 62, 63 |
| Disease duration (mo) | 22, 16 | 60, 62 |
| Follow-up duration (mo) | 11, 4 | 10, 4 |
| **Primary ANA pattern**, N (%) | | |
| Homogenous | 0 (0) | 2 (29) |
| Speckled | 4 (57) | 3 (43) |
| Nucleolar | 3 (43) | 2 (29) |
| **SSc-specific antibodies**, N (%) | | |
| Scl-70 | 0 (0) | 2 (29) |
| RNA Polymerase III | 1 (14) (N = 2) | 3 (43) |
| Treatment by intrinsic subset | | |
| **Inflammatory** | N = 7 | N = 2 |
| MMF-treated | 6 (1 concurrent minocycline) | 1 |

| | | |
|---|---|---|
| MMF-ever treated (additional therapies) | 1 (CTX, MTX, IVIG)[†] | 0 |
| **Normal-like** | N = 0 | N = 1 |
| MMF-treated | 0 | 1 |
| MMF-ever treated | 0 | 0 |
| **Fibroproliferative** | N = 0 | N = 4 |
| MMF-treated | 0 | 4 (1 concurrent MTX) |
| MMF-ever treated | 0 | 0 |
| **Echocardiography** | | |
| LVEF (%) | 63, 3 (N = 6) | 63, 3 |
| LV mass (g/m$^2$) | 76, 12 (N= 5) | 80, 13 |
| TAPSE (cm) | 2.6, 0.4 (N = 6) | 2.3, 0.5 |
| RV FAC | 0.47, 0.02 (N = 6) | 0.47, 0.05 |
| PASP (mmHg)** | 26, 4 (N = 5) | 34, 5 (N = 5) |
| LV diastolic function (n, %) | | |
| Normal | 2 (33) (N = 6) | 3 (43) |
| Abnormal | 2 (33) (N = 6) | 3 (43) |
| Indeterminate | 2 (33) (N = 6) | 1 (14) |
| **Pulmonary Function Test** | | |
| FVC % Predicted | 83, 17 | 71, 6 |
| FEV1 % Predicted | 86, 17 | 72, 7 |
| FEV1/FVC % Predicted | 83, 9 | 82, 10 |
| TLC % Predicted | 93, 11 | 81, 10 |
| DLCO % Predicted | 66, 20 | 59, 14 |
| **HRCT Exam** | | |

| | | |
|---|---|---|
| Total Lung Disease Score | 4.83, 2.48 | 10.86, 8.76 |

MRSS = modified Rodnan skin score, Disease duration=months between biopsy date and first non-Raynaud symptom, centromere ANA pattern and anticentromere antibodies were not observed in study cohort, MMF-treated=MMF treatment at baseline biopsy and/or during follow-up, CTX=cyclophosphamide, MTX=methotrexate, IVIG=intravenous immunoglobulin, LVEF=left ventricular ejection fraction, LV=left ventricle, TAPSE=tricuspid annular plane systolic excursion, RV FAC=right ventricular fractional area change, PASP=pulmonary artery systolic pressure, FVC=forced vital capacity, FEV1=forced expiratory volume in one second, TLC=total lung capacity, DLCO=diffusing capacity for carbon monoxide. Total lung disease scoring for each of 5 lung lobes assessed: 0=No disease, 1=0-5 (minimal disease but not normal), 2=5-25, 3=26-50, 4=51-75, 5=76-100% involvement. * P=0.02, **P=0.03. [†]MMF was discontinued after one month secondary to side effects.

## Supplemental Table 5: Significant annotations for genes with high expression in improvers

| Term | Count | % | P-value | Benjamini |
|---|---|---|---|---|
| lymph_normal | 21 | 26.3 | 4.8E-05 | 0.004 |
| cartilage | 15 | 18.8 | 1.6E-04 | 0.028 |
| white blood cells_monocyte | 17 | 21.3 | 3.1E-04 | 0.035 |
| ovary_normal | 25 | 31.3 | 2.9E-03 | 0.043 |
| skin tumor_disease | 22 | 27.5 | 2.4E-03 | 0.045 |

## Supplemental Table 6: Significant annotations for genes with low expression in improvers

| Term | Count | % | P-value | Benjamini |
|---|---|---|---|---|
| retina_central retina | 30 | 14.4 | 9.0E-05 | 0.010 |
| brain_Anaplastic GradeII Astrocytoma | 31 | 14.8 | 8.4E-05 | 0.014 |
| regulation of Ras protein signal transduction | 12 | 5.7 | 1.5E-05 | 0.018 |
| brain_null | 34 | 16.3 | 2.2E-04 | 0.019 |
| brain_astrocytoma grade II | 25 | 12.0 | 5.2E-04 | 0.036 |
| regulation of cell communication | 26 | 12.4 | 9.2E-05 | 0.036 |
| cerebellum_normal cerebellum | 32 | 15.3 | 7.1E-04 | 0.040 |
| brain_anaplastic astrocytoma grade III | 27 | 12.9 | 1.3E-03 | 0.044 |
| regulation of small GTPase mediated signal transduction | 12 | 5.7 | 7.9E-05 | 0.046 |

**Supplemental Table 7: Annotations for genes whose expression increased during MMF treatment in the improvers**

| Term | Count | % | P-value | Benjamini |
|---|---|---|---|---|
| protein binding | 186 | 51.0 | 3.4E-06 | 0.002 |
| extracellular matrix | 21 | 5.8 | 1.4E-05 | 0.005 |
| proteinaceous extracellular matrix | 19 | 5.2 | 5.7E-05 | 0.009 |
| binding | 249 | 68.2 | 3.2E-04 | 0.081 |

**Supplemental Table 8: Annotations for genes whose expression decreased during MMF treatment in the improvers**

| Term | Count | % | P-value | Benjamini |
|---|---|---|---|---|
| intracellular | 111 | 77.6 | 8.1E-09 | 1.6E-06 |
| intracellular part | 108 | 75.5 | 3.2E-08 | 3.1E-06 |
| organelle | 92 | 64.3 | 1.4E-05 | 5.5E-04 |
| intracellular organelle | 92 | 64.3 | 1.3E-05 | 6.3E-04 |
| organelle fission | 12 | 8.4 | 2.8E-06 | 6.6E-04 |
| condensed chromosome, centromeric region | 7 | 4.9 | 1.1E-05 | 6.9E-04 |
| M phase of mitotic cell cycle | 12 | 8.4 | 2.3E-06 | 7.1E-04 |
| kinetochore | 7 | 4.9 | 2.6E-05 | 8.4E-04 |
| mitotic cell cycle | 15 | 10.5 | 2.0E-06 | 9.4E-04 |
| chromosome, centromeric region | 8 | 5.6 | 4.5E-05 | 1.2E-03 |
| condensed chromosome | 8 | 5.6 | 5.7E-05 | 1.4E-03 |
| condensed chromosome kinetochore | 6 | 4.2 | 7.8E-05 | 1.7E-03 |
| nuclear division | 12 | 8.4 | 1.9E-06 | 1.8E-03 |
| mitosis | 12 | 8.4 | 1.9E-06 | 1.8E-03 |
| membrane-bounded organelle | 82 | 57.3 | 1.4E-04 | 2.3E-03 |
| intracellular membrane-bounded organelle | 82 | 57.3 | 1.3E-04 | 2.4E-03 |
| spindle | 8 | 5.6 | 1.3E-04 | 2.5E-03 |
| M phase | 13 | 9.1 | 1.7E-05 | 3.0E-03 |
| cytoplasm | 76 | 53.1 | 2.8E-04 | 4.2E-03 |
| cell cycle phase | 14 | 9.8 | 3.5E-05 | 5.4E-03 |
| cell cycle process | 16 | 11.2 | 5.9E-05 | 7.8E-03 |
| intracellular organelle part | 50 | 35.0 | 5.7E-04 | 7.9E-03 |
| organelle part | 50 | 35.0 | 6.6E-04 | 8.5E-03 |
| macromolecular complex | 40 | 28.0 | 8.3E-04 | 1.0E-02 |
| NOD-like receptor signaling pathway | 6 | 4.2 | 1.7E-04 | 1.1E-02 |
| nucleus | 56 | 39.2 | 1.2E-03 | 1.4E-02 |
| cell | 121 | 84.6 | 1.9E-03 | 1.9E-02 |
| cell part | 121 | 84.6 | 1.9E-03 | 2.0E-02 |
| cytoplasmic part | 52 | 36.4 | 5.2E-03 | 4.9E-02 |
| cytosol | 20 | 14.0 | 5.5E-03 | 4.9E-02 |
| intracellular non-membrane-bounded organelle | 32 | 22.4 | 5.8E-03 | 5.0E-02 |
| non-membrane-bounded organelle | 32 | 22.4 | 5.8E-03 | 5.0E-02 |